"A STUDY ON THE SERUM LEVELS OF FIBRINOGEN AMONG SMOKERS AND ITS CORRELATION WITH THE DURATION AND AMOUNT OF SMOKING"

Dissertation submitted in partial fulfillment of the

Requirement for the award of the Degree of

DOCTOR OF MEDICINE - BRANCH VII

GENERAL MEDICINE

APRIL 2015

TIRUNELVELI MEDICAL COLLEGE HOSPITAL

THE TAMIL NADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI ,TAMIL NADU

CERTIFICATE

This is to certify that the Dissertation entitled **"A STUDY ON THE SERUM LEVELS OF FIBRINOGEN AMONG SMOKERS AND ITS CORRELATION WITH THE DURATION AND AMOUNT OF SMOKING"** submitted by **Dr.R.SAYEE VENGATESH** to The Tamilnadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment for the award of M.D.Degree(GENERAL MEDICINE) is a bonafide work carried out by him under my guidance and supervision during the academic year 2012-2015. This dissertation partially or fully has not been submitted for any other degree or diploma of this university or other.

Prof.Dr.RAVICHANDRAN. MD.,
Unit Chief, UNIT III,
Department of Medicine,
Tirunelveli Medical College ,
Tirunelveli – 627011.

Prof. Dr.VAIRAMUTHURAJU. MD
Professor and HOD,
Department of Medicine,
Tirunelveli Medical College,
Tirunelveli – 627011.

The Dean,
Tirunelveli Medical College,
Tirunelveli – 627 011.

DECLARATION

I**, Dr.R.SAYEE VENGATESH**, solemnly declare that the Dissertation titled **"A STUDY ON THE SERUM LEVELS OF FIBRINOGEN AMONG SMOKERS AND ITS CORRELATION WITH THE DURATION AND AMOUNT OF SMOKING"** has been prepared by me.

This is submitted to the Tamilnadu Dr.M.G.R. Medical University, Chennai, in partial fulfillment of the regulations for the award of MD Degree Branch VII (MEDICINE).

It was not submitted to the award of any degree/diploma to any University either in part or in full previously.

Place: TIRUNELVELI

Date:

DR.R.SAYEE VENGATESH,

POST GRADUATE,

M.D.GENERAL MEDICINE,

TIRUNELVELI MEDICAL COLLEGE HOSPITAL

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INSTITUTIONAL RESEARCH ETHICS COMMITTEE

TIRUNELVELI, STATE OF TAMILNADU, SOUTH INDIA PIN 627011

91-462-2572710 EXT; 91-462-2572444; 91-462-2576705; 91-462-2572613-18

online@tvmc.ac.in, tirec@tvmc.ac.in, www.tvmc.ac.in

CERTIFICATE OF REGISTRATION & APPROVAL OF THE TIREC REF NO: 404/GM/2013/29.03.13

PROTOCOL TITLE: A Study of the Serum Fibrinogen Levels among Smokers and its Correlation with the Quantity and Duration of Smoking

NAME OF PRINCIPAL INVESTIGATOR: R.Sayee Vengatesh

DESIGNATION OF PRINCIPAL INVESTIGATOR: Post Graduate Resident

DEPARTMENT & INSTITUTION: Department of General Medicine, Tirunelveli Medical College

Dear Dr. R.Sayee Vengatesh, *the Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during the IEC meeting held on* 29.03.2013

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1.	TIREC Application Form	☐
2.	Study Protocol	☐
3.	Department Research Committee Approval	☐
4.	Patient Information Document and Consent Form in English and Vernacular Language	☐
5.	Investigator's Brochure	☐
6.	Proposed Methods for Patient Accrual Proposed	☐
7.	Curriculum Vitae of the Principal Investigator	☐
8.	Insurance /Compensation Policy	☐
9.	Investigator's Agreement with Sponsor	☐
10.	Investigator's Undertaking	☐
11.	DCGI/DGFT approval	☐
12.	Clinical Trial Agreement (CTA)	☐
13.	Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA)	☐
14.	Clinical Trials Registry-India (CTRI) Registration	☐

THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 3weeks before for renewal / extension of the validity
4. An annual status report should be submitted.
5. The TIREC will monitor the study
6. At the time of PI's retirement/leaving the institute, the study responsibility should be transferred to a person cleared by HOD
7. The PI should report to TIREC within 7 days of the occurrence of the SAE. If the SAE is Death, the Bioethics Cell should receive the SAE reporting form within 24 hours of the occurrence.
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   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. The PI must comment how proposed amendment will affect the ongoing trial. Alteration in the budgetary status, staff requirement should be clearly indicated and the revised budget form should be submitted.
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented.
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   g. Any deviation/violation/waiver in the protocol must be informed

STANDS APPROVED UNDER SEAL

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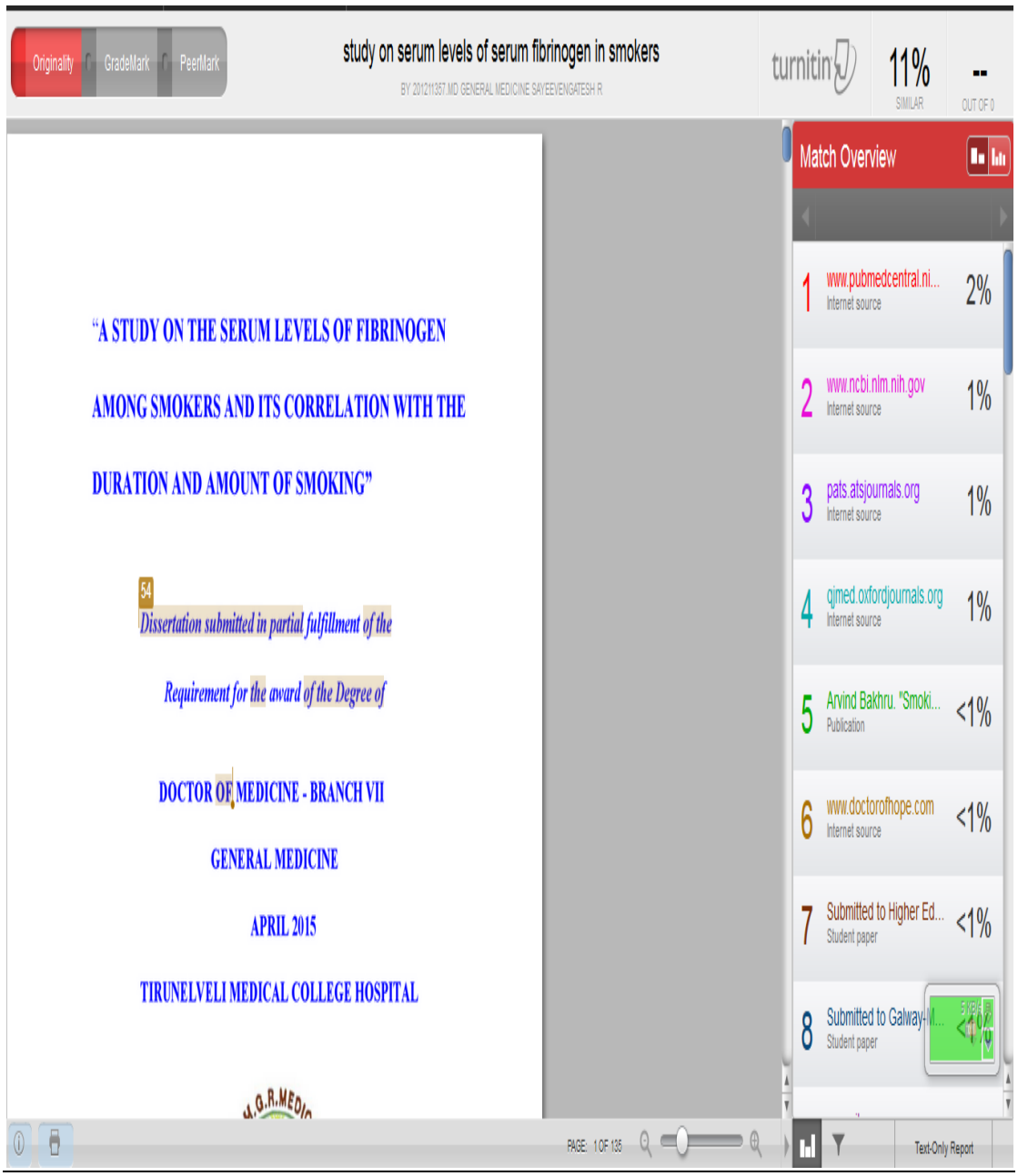
Registrar, TIREC
Tirunelveli Medical College, Tirunelveli – 627011
State of Tamilnadu, South India

Dr.V.Ramasubramanian MD DM
Member Secretary, TIREC
Tirunelveli Medical College, Tirunelveli – 627011
State of Tamilnadu, South India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CONTENTS

A STUDY OF SERUM LEVELS OF FIBRINOGEN IN SMOKERS AND ITS CORRELATION WITH TYPE , AMOUNT AND DURATION OF SMOKING:

Abstract

Background: According to many studies, serum levels of fibrinogen is found to be higher in smokers than in non smokers.This may contribute to increase in the incidence of myocardial infarction and cerebro vascular accidents in future.

Aims: To find out the levels of serum fibrinogen in smokers and non smokers and compare the levels of serum fibrinogen in smokers according to their type, amount and duration of smoking.

Materials and methods: 100 patients and their attenders , who did not fit into the exclusion criteria were taken as the study population. The control group had 50participants. The serum fibrionogen levels were measured using the clauss method.

Results: Out of the 100cases smokers and 50 non smokers , smokers have higher levels of serum fibrinogen than non smokers. The levels of serum fibrinogen were also higher in persons who smoked for many years and higher pack years.

Conclusion: In this study, smokers have higher levels of serum fibrinogen than non smokers. The levels of serum fibrinogen were also higher in persons who smoked for many years and higher pack years. The incidence of thrombo embolic episodes were also more in smokers.

Key words: serum fibrinogen , smoking , cigarette smoking , myocardial infarction.

STUDY ON SERUM LEVELS OF SERUM FIBRINOGEN ON SMOKERS:

INTRODUCTION:

Smoking produces a state of chronic inflammation which is mainly due to increased levels of free radicles. Free radicles produces an oxidative stress thisdamages mainly the cardio vascular system. blood vessels and central nervous system are also affected. The cell damage anddamage recycling process are done by antioxidants. In smokers the antioxidants levels are reduced which

causesimproper cell repair and damage. Smoking causes narrowing of airways which also affects pulmonary function test. cigarettes also contain carcinogens . This predisposes them to many cancers. Smoking is also associated with low levels of high density lipoprotein. This increases the risk of atherosclerosis. Smoking is a mediator of inflammation . Therefore it increases the levels of acute phase reactants. One among them is fibrinogen. Fibrinogen is synthesized by liver. Apart from its major role in coagulation cascade it is also produced in various inflammatory conditions as an acute phase reactant. Smoking as a main cause for chronic inflammation it increases the levels of serum fibrinogen.

Increasedfibrinogen keeps the blood in a hyper coagulated state. Since hyper coagulation causes arterial and venous thrombosis increased fibrinogen is associated with major cerebro and cardio vascular events. Our aim of study is to measure the levels of serum fibrinogen among the smokers and comparing the level of fibrinogen in smokers based on their duration , amount and type of smoking.

AIM

AIM:

- **To measure the level of serum fibrinogen in smokers.**
- **To study the relationship between duration of smoking and the level of serum fibrinogen.**
- **To study the relationship between the pack years and the levels of serum fibrinogen.**
- **To study the relationship between the type of smoking and the levels of serum fibrinogen.**

REVIEW OF LITERATURE

REVIEW OF LITERATURE:

Fibrinogen:

Fibrinogen is one of the clotting factors synthesized by liver. It plays important role in

i. Coagulation pathway.

ii. As an acute phase reactant plays an important role in inflammatory pathway.Increased levels of serum fibrinogen is associated with increased risk of cardio vascular , cerebro vascular accidents and other thrombo embolic complications.

Plasma levels of fibrinogen is increased by

i. Age

ii. Diabetes

iii. Hyperlipidemia

iv. Hypertension

v. Smoking

vi. Low density lipoprotein

vii. Post menopausal state

viii. Body mass index

ix. Leukocytosis

Plasma levels of fibrinoged is decreased by

i. Moderate consumption of alcohol

ii. Increased levels of HDL

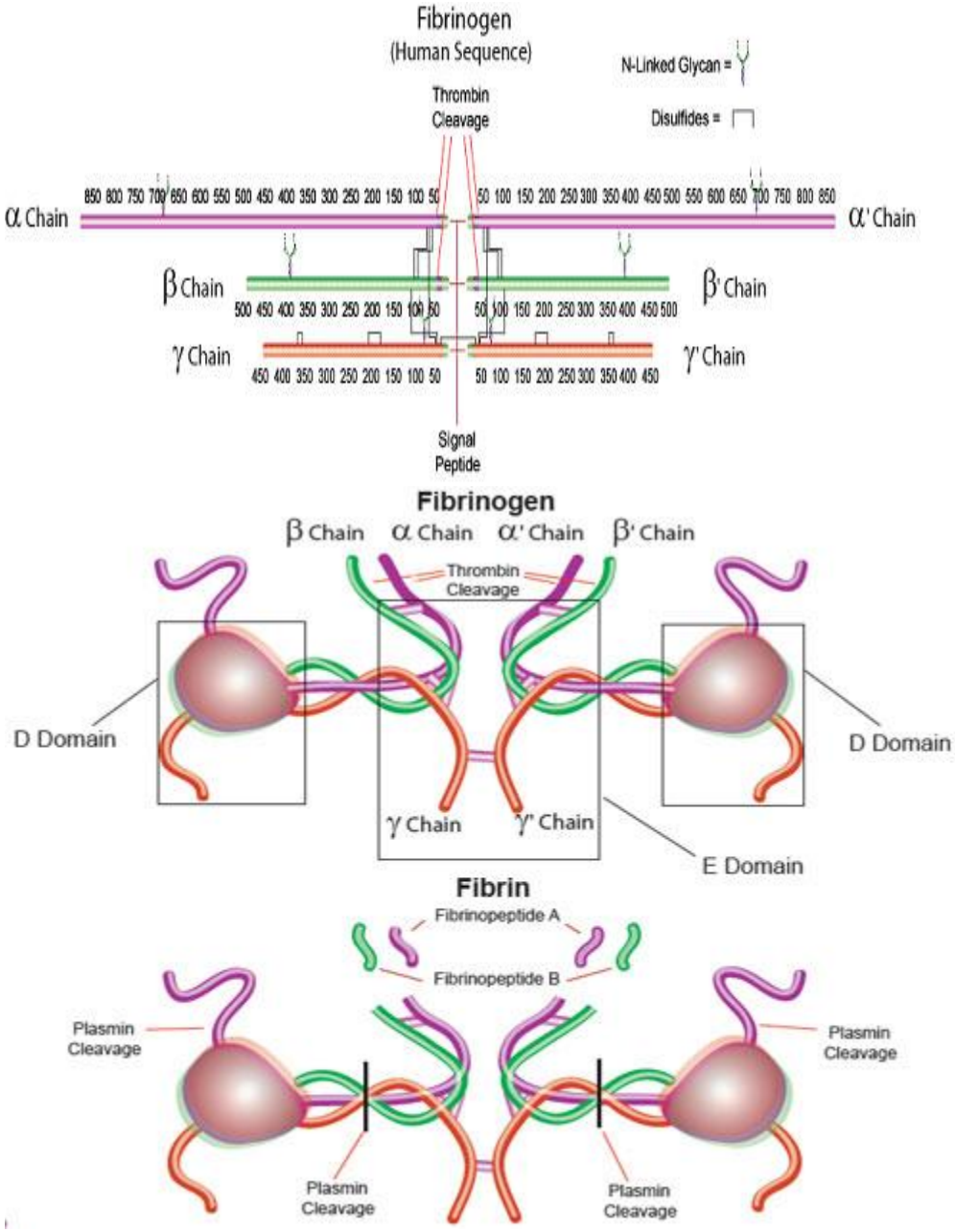
iii. Hormone replacement therapy

Fibrinogen is a glycoprotein . it is synthesized by liver[3]. Its molecular weight is 340 Kda[2]. Half life of fibrinogen is 100 hrs. normal serum levels of fibrinogen is 200 to 400 mgs/ dl. Its structure is composed of three pairs of three peptide chains .

i. Alpha chains

ii. Beta chains and

iii. Gamma chains



The chains are non identical. The chains are connected to each other by disulfide linkages.Fibrinogen is the precursor of fibrin . fibrin is essential for clotting.

Fibrinogen is essential in the pathophysiology of

i. Inflammation

ii. Coagulation

iii. Thrombus formation[4]

Fibrinogen and inflammation:

Fibrinogen promotes the binding of leukocytes to endothelium and also activation of leukocytes. It is mainly through binding with receptors present in leukocytes and endothelial cell. By binding with ICAM-1 it promotes the binding of neutrophils and monocytes with endothelial cells. Fibrinogen causes activation of leukocytes by increasing the intra cellular levels of calcium and also by increasing the levels of neutrophil activation markers.[5][6] As a result of this there is increased phagocytosis and antibody mediated cytotoxicity. Fibrinogen also causes cell to cell interaction and also cell to matrix interaction.

Fibrinogen and thrombosis:

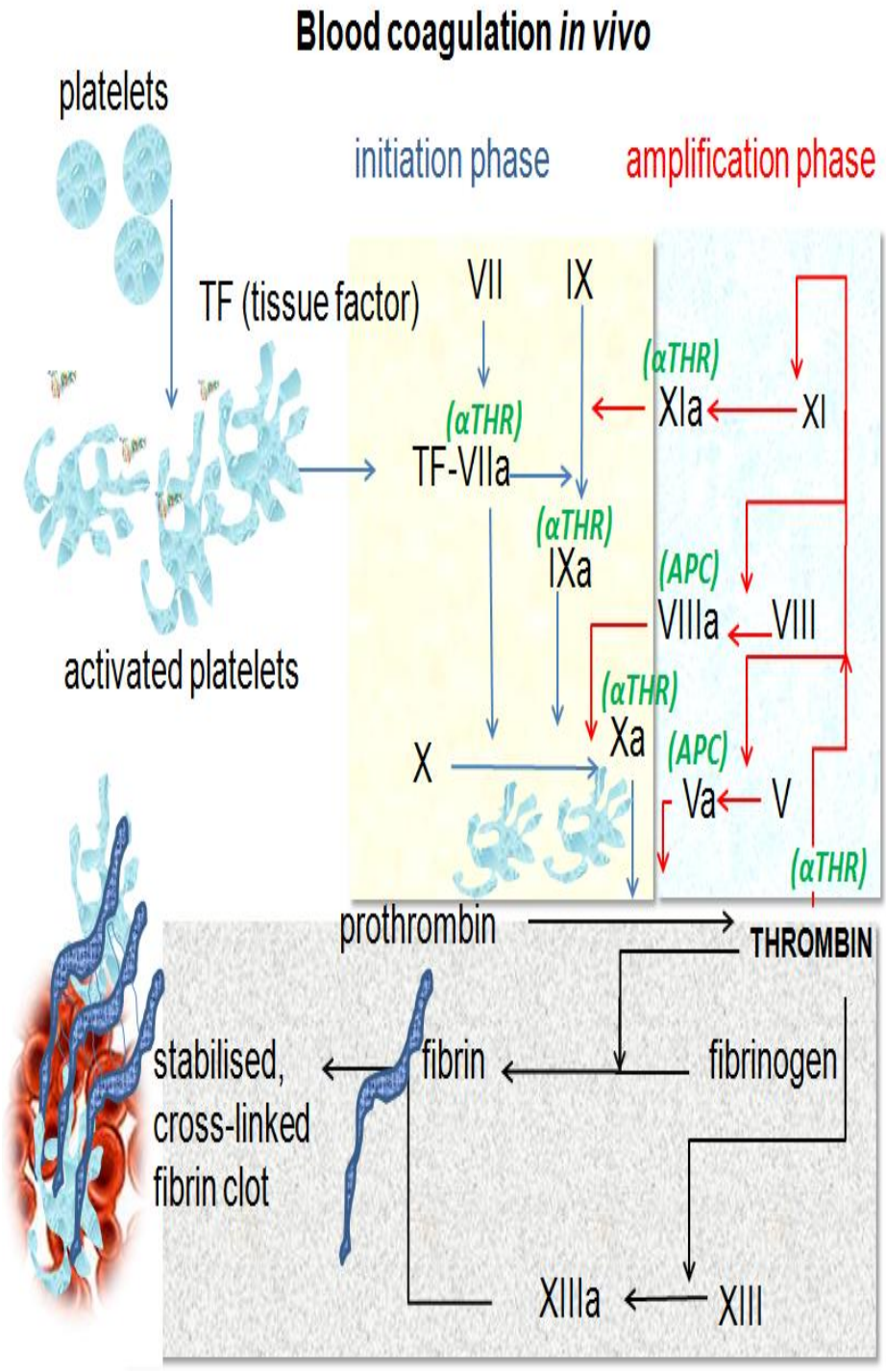
Fibrinogen binds with platlets surface receptors gpiib – iiia and promotes platlets aggregation fibrinogen plays an important role in coagulation pathway by participating in both intrinsic and extrinsic pathway. When there is damage to endothelial cells and causes the release of tissue thromboplastin which inturnactivates factor vii which causes the activation of extrinsic pathway. When blood comes into contact with foreign body activation of factor xii to xii a which causesthe activation of intrinsic pathway. Both pathways merges into common pathway which causes the activation of conversion of thrombinogen to thrombin.Thrombin converts fibrinogen into fibrin which is the final step in coagulation[7].

Finally activation of factor xiii causes the stabilization of clot.

Fibrinogen and atherogenesis:

Fibrinogen plays dual role in atherogenesis. It causes both formation of plaques and also growth of plaques.

Fibrinogen is seen either in the surface of the plaque cap or within the cap or seen evenly distributed throughout the atheromatous plaque. Inside intima Fibrinogen binds with fibronectin [8][9].



Fibronectin promotes cell migration and adhesion inside intima. Fibrin degradation products also promotes cell

proliferation and mitogenesis. Inside stable plaque fibrinogen binds tightly with LDL and helps in plaque extension.As a result of these process there is progression of atherogenesis

Determinants of plasma fibrinogen levels:

The level of serum fibrinogen is determined by 2 factors.

i. Genetic

ii. Environmental

Genetic:

Synthesis of fibrinogen is under genetic control.The long arm of chromosome 4 synthesises the three chains.The direction of transcription of beta gene is opposite to that of alpha and gamma gene.Variation in the locus of fibrinogen locus leads to variation in plasma fibrinogen levels.The synthesis of beta chain is the rate limiting step in the synthesis of plasma fibrinogen.Recently various polymorphisms have been found that affect the plasma fibrinogen value.These polymorphisms can be identified by Restriction Fragment Length Polymorphism(RFLP)

and also by Single Stranded Conformation Polymorphism (SSCP). One of the strongest genetic variations associated with increased plasma fibrinogen is the 455G/A mutation in the promoter region of fibrinogen gene. One study suggests that B1B1 genotype is associated with fibrinogen level of 2.74g/dl whereas B2B2 phenotype is associated with serum fibrinogen level of 3.69g/dl[10][11]. This level is considered as the cut off level for the development of ischemic heart disease.

Environmental factors:

Serum fibrinogen value is influenced by many environmental factors and also patient's lifestyle.

i. **Smoking**

Smoking is associated with increase in the level of serum fibrinogen value.The effect is mainly dose dependent. There is inverse relationship between serum fibrinogen value and time since stopping the habit of smoking[12].

ALCOHOL:

Moderate consumption of alcohol is associated with lower

levels of serum fibrinogen.

Factors associated with higher levels of fibrinogen:

- Female sex
- Black race
- Increase in age
- Obesity
- Elevated cholesterol
- Smoking
- Physical inactivity
- Oral contraceptives
- Menopause
- Stress
- Low socioeconomic status

Factors associated with lower levels of fibrinogen:

- Male sex
- Young age
- Stop the habit of smoking
- Regular aerobic exercises

- Reduction of weight

- Mediocre consumption of alcohol

- Hormone replacement therapy.

Interventions to reduce serum fibrinogen levels:

Beneficial:

- Cessation of smoking
- Drugs: fibrates

May be beneficial:

- Moderate consumption of alcohol
- Weight loss
- Lowering of blood pressure.

Not beneficial:

- Statins

Gender:

Studies shown that serum fibrinogen is higher in females than in males.This value is constant irrespective of the age pregnancy and use of oral contraceptives

Age:

Serum fibrinogen value increases as the age advances[13][14]. This is mainly due to slower rate of disposal of fibrinogen than the increased production.Body mass index and body habitus: Serum fibrinogen increases with increase in body weight Waist circumference , hip circumference and waist hip ratio.Serum fibrinogen levels in persons with BMI > 30kg/m2 is higher when compared to persons with BMI <25 kg/m2. Serum fibrinogen value decreases after surgicalcorrection of obesity after 6 months[15]

Metabolic syndrome:

This is charerterised by the presence of 3 or more of the following.

i. High-density lipoprotein-cholesterol < 1.13 mmol/l
ii. Triglycerides >1.80 mmol/l;
iii. Glucose >5.5 mmol/l;
iv. Diastolic blood pressure _90mm Hg.

Serum fibrionogen increases with increase in any one of the above parameters.

Acute exercise:

Acute exercise has no effect on serum fibrinogen value. But in patients with vascular diseases acute exercise increases the levels of serum fibrinogen[16].

Regular exercise:

Regular exercise reduces the levels of serum fibrinogen . One study proved that 4 weeks of regular exercise lowers the levels of serum fibrinogen[17].Serum fibrinogen values returns to normal values after resumption of sedentary activities. Men and women who have higher levels of activity has lower levels of fibrinogen.

Seasonal variation:

Fibrinogen value changes with season. Its value rises in persons during winter season and decreases during summer season.[18][19][20][21][22]

Vitamin C and infection:

Decreased levels of body vitamin c is associated with increased levels of serum fibrinogen.Upper respiratory tract infection is associated with increased levels of

serum fibrinogen. Chlamydia and helicobacter infections are associated with increased incidence of coronary heart disease. Whether their effect is mediated through increased levels of fibrinogen is unknown.

Socio economic status:

Socio economic status is inversely related to serum levels of fibrinogen.

Hormonal status:

Post menopausal status is associated with increased serum levels of fibrinogen[23] . Oral contraceptive usage is associated with increased serum levels of serum fibrinogen.Hormone replacement treatment in post menopausal women is associated with lower levels of serum fibrinogen[24].

Alcohol:

There is U shaped association between serum levels of fibrinogen and alcohol consumption[25]. Moderate consumption of alcohol is associated with lower levels of serum fibrionogen value but consumption of more than 60 g/ day is associated with higher fibrinogen levels. Higher consumption is associated with high bp and

development of atrial fibrillation which increases the levels of fibrinogen.

Smoking:

Smoking is the most dangerous health hazard. Smoking took part in the entire process of atherosclerosis from endothelial dysfunction to thrombogenesis both active and passive smoking contributes to the pathogenesis of harmful effects. Even smokeless cigarettes can also cause damage. It is mainly contributed to the oxidative stress produced by the toxic substances present in the smoke.

Smoking is in the form of
1. cigarettes
2. bedis
3. cigars
4. hookahs
5. vaporizers
6. bongs.

Tobacco smoking is the most common type of smoking . Next is cannabis smoking.

Smoke:

Smoke is composed of 2 phases.

i. Tar phase

ii. Gas phase[26]

Tar phase is the particulate matter present in smoke which gets trapped while passing through the Cambridge gas filter.Gas phase is the substance that passes through the gas filter.Tar phase consists of $>10^{17}$ free radicals/g, and the gas phase consists of $>10^{15}$ free radicals/puff. The free radicles present in tar phase is long living (hours to months) while the free radicles present in gas phase is short living (few seconds).

Smoke is also of 2 types.

i. Main stream stroke

ii. Side stream stroke.[27]

The smoke that enters smokers mouth through the end of the cigarette is called main stream stroke[29]. The smoke that emerges from the burning end of the cigarette is called as side stream stroke[28]. Mainstream stroke contains gas 90% and tar particles 10% Passive smoking

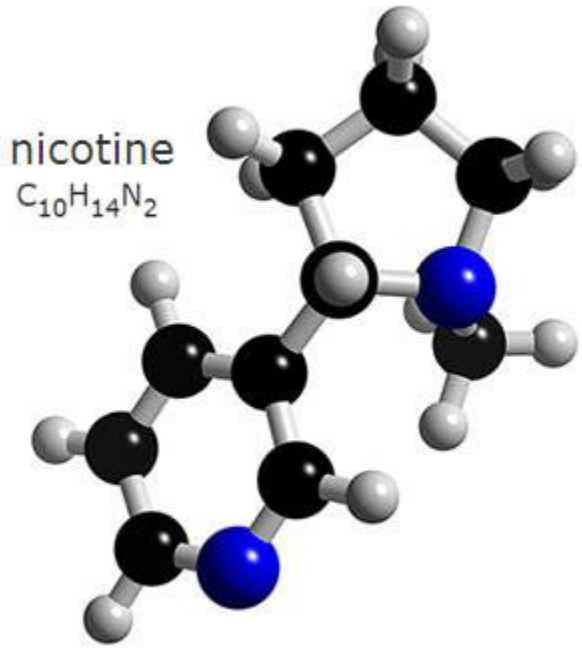
is mainly composed of side stream smoke 85%

Side stream smoke contains more toxic substances than main stream smoke.Smoking leads to atherosclerosis by many ways. The outcome of atherosclerosis may be in the form of unstable angina , acute coronary syndrome sudden death and stroke. It also involves aorta and peripheral vessels leading to intermittent claudication and aortic aneurysm. Smoking promotes atherosclerosis by 3 main ways.

- Inflammation
- Vasomotor dysfunction
- Modification of lipid levels

Vasomotor dysfunction:

The earliest way by which smoking produces atherosclerosis is by causing impairment in vasodilation. This is seen in both active as well as in passive smoking. Cigarette smoking impairs endothelium dependend vasodilation in both macro vascular and micro vascular circulation. Nitric oxide is the main vasodilatory substance present in



our body. Smoking decreases the availability of nitric oxide to endothelial cells besides vasodilation smoking also plays an important role in regulation of inflammation , leukocyte adhesion , thrombosis and platlet activation.

Smoking and inflammation:

Inflammation is the second step in atherogenesis. Smoking provokes inflammation by causing increased expression of cell adhesion molecules on the surface of both endothelial cells and leukocytes mainly ICAM 1 andVCAM 1. Smoking also increases leukocyte count and also promotes cell to cell interaction. Thus smoking

adds fuel to the fire of inflammation.

Smoking and lipid profile:

Smoking promotes atherosclerosis by altering lipid profile. It increases triglycerides , low density lipoprotein but lowers high density lipoprotein. These effects are mainly due to insulin resistance. Smoking promotes oxidation of LDL and also causes the synthesis of auto antiobodies to LDL. Endothelial cells identified from smokers have higher levels of oxidized LDL. Smokers have lower levels of paroxanase an enzyme involved in protecting the oxidization of LDL.

Smoking and genetic predisposition:

Genetic predisposition also affects the rate of development of atherogenesis in individuals with smoking. Polymorphism of CYP1A1 or endothelial nitric oxide synthetase 4 polymorphism alters the development of atherogenesis.

Smoking and thrombosis:

Smoking promotes thrombosis formation leading to acute myocardial infarction. Main mechanism is by plaque rupture and formation of thrombus on plaque. It also causes vasospasm there by causing prinzmetal angina. By contrast cessation of smoking reduces the risk of thrombosis. At the end of 5 years ex smokers have same risk as that of non smokers. A study by sergeant, shepard , glantz at 52nd annual American conference of cardiology confirmed this. Smoking is the most preventable common cause of mortality and morbidity all over the world. Smoking is responsible for 4,43,000 deaths all over world per year.This includes those who are affected by second hand smoking like the babies who are affected by maternal smoking. Cigarette smoking contains more than 7000chemicals out of which 69 are found to be carcinogens. The most common cause of death due to smoking is attributed to lung cancer and next one to COPD. Age is the most important risk factor for the developmentof coronary heart disease. Apart from age smoking is the most common cause. Among the

persons with smoking habit ischemic heart disease is the leading cause of mortality. The prevalence of smoking is very common in developing countries. Habit of smoking is decreased in developed countries. China is the country which has the largest number of smokers. Second one is India. Smoking is responsible for the death of more than two billion per year. Even among the non smokers passive smoking is responsible for the most common cause of mortality from ischemic heart disease. Smoking's adverse effects depends upon many features. Amount of smoking ,type of smoking , duration . smokers have high risk of developing many problems compared to nonsmokers. Among smokers light smokers have less risk compared to heavy smokers. Risks increases with the quantity of smoking daily. Smoking was initially very prevalent among men . but nowadays its prevalence increased among women. If a women takes oral contraceptives along with smoking she had higher risk compared to women who is not taking oral contraceptive pills. Smoking causes rise in blood pressure.

It increases both systolic and diastolic blood pressure. It increases sympathetic tone. It promotes the formation of atherosclerosis . it causes the risk of atherosclerosis rupture. It increases the formation of thrombosis and leads to reduced blood flow to myocardium. This leads to the adverse cardio vascular side effects. It increases the oxidation of low density lipoproteins. It reduces the synthesis of nitric oxide . nitric oxide is also called as endothelium derived relaxing factor. It increases tissue type plasminogen activator. It increases the tissue pathway factor inhibitor. Smoking increases fibrionogen. Smoking increases homocysteine. It increases platlet aggregation.smoking increases the risk of coronary spasm. It is associated with increased risk of ventricular arrhythmias. It increases insulin resistance. Stopping smoking is the most important protocol in the treatment of coronary heart disease. Cigarette smoking stopping is associated with reduced risk of heart disease. The incidence is about 36%. This is not changed by age. This is not also affected by race , age and gender and ethenicity. Cigarette smoking cessation is associated

with more beneficial effect when compared to taking aspirin. This is also superior to beta blockers, statins and ace inhibitors. Smoking cessation have much benefits when they are combined with healthy exercise. They also have increased benefits when smoking abstinence is combined with healthy foods. Good results were obtained when nicotine chewing gums are used instead of cigarettes. But low smoke cigarettes does not decreases the risk of smoking related problems. stopping the habit of smoking is associated with reduced incidence of cardio vascular problems. This is confirmed by many trials. But the risk of development of various cancers is unchanged. There is increased risk for developing cancer of the pancreas. Similarly there is increased risk of developing chronic obstructive pulmonary disease even after stopping the habit of smoking.

Nicotine:

The main component of smoke is nicotine. It is an alkaloid. It is mainly present in the family of solanaceae

.

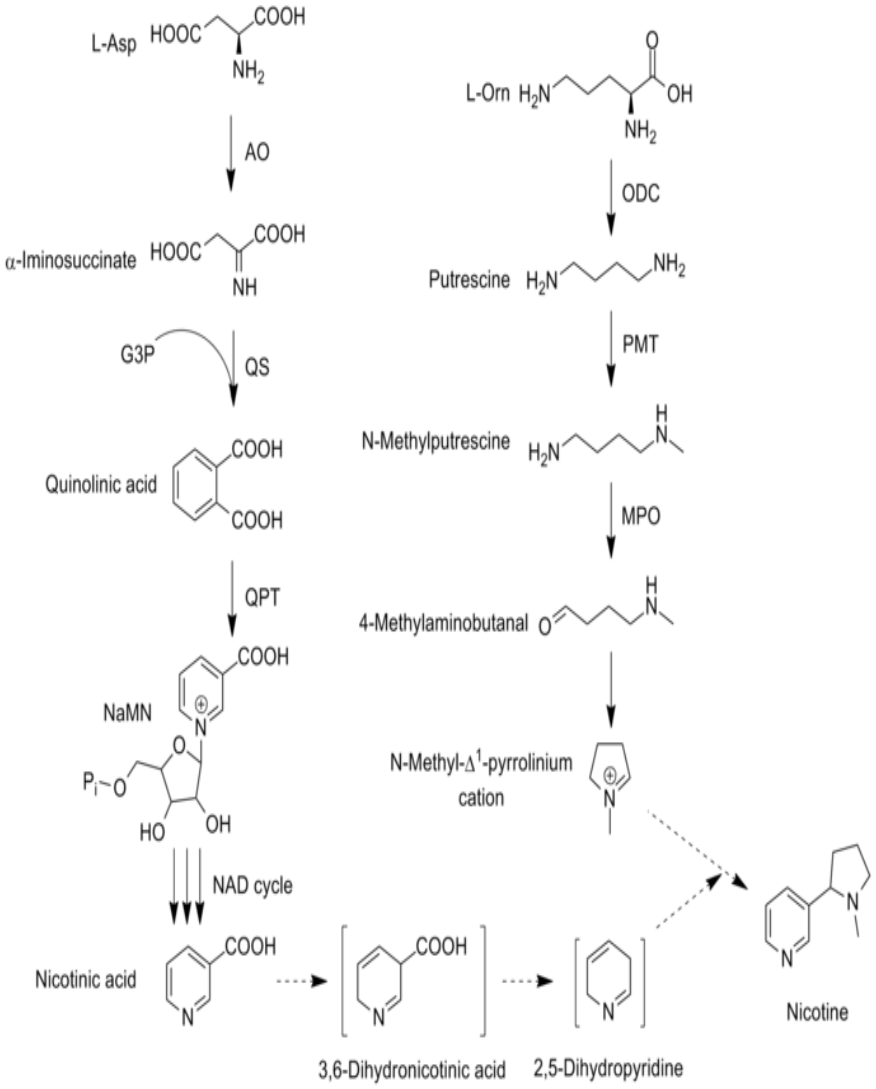
It has action that resembles cholinergic activities. It acts on the nicotinic receptors of the cholinergic nervous system[30]. At very low doses it stimulates the central nervous system. But in high doses it affects the central nervous system. This causes many unwanted side effects. This substance is responsible for the addiction of persons to the cigarettes. This name is derived from the name of the tobacco plant. Tobacco plant is called as Nicotiana. Adolf pinner described its molecular formula[31]. Nicotine is a substance that is soluble in water. It is not soluble in water. It is miscible in water. The salts of nicotine is soluble in water. The levo rotatory form of this compound is more active than the other form.

Synthesis of nicotine:

Nicotine is synthesized from 2 main compounds. They are

1. Niacin
2. Pyrollidium ion.

Synthesis of niacin is from NAD pathway. Synthesis of pyrollidium ion is from tropane pathway[32].



Nicotine once it smoked reaches the alveoli. From there it is rapidly absorbed from capillary system. Then it reaches the brain by crossing the blood brain barrier. The half life of nicotine is found to be around 2 hours[33]. Nicotine that enters the human body is dependent on the following

1. Type of smoked substance like cigars , beedis.

2. Presence or absence of filters.

Nicotine acts on the cholingeric receptors present in the central nervous system. They are also present in adrenal medulla. They are also present in autonomic ganglia. It is mainly metabolized by the enzymes present in the liver. They are called as cytochromes.The active product of nicotine is cotinine. The main end products are

1. Cotinine
2. Nor nicotine
3. Nicotine glucuronide.

They are mainly excreted through urine.

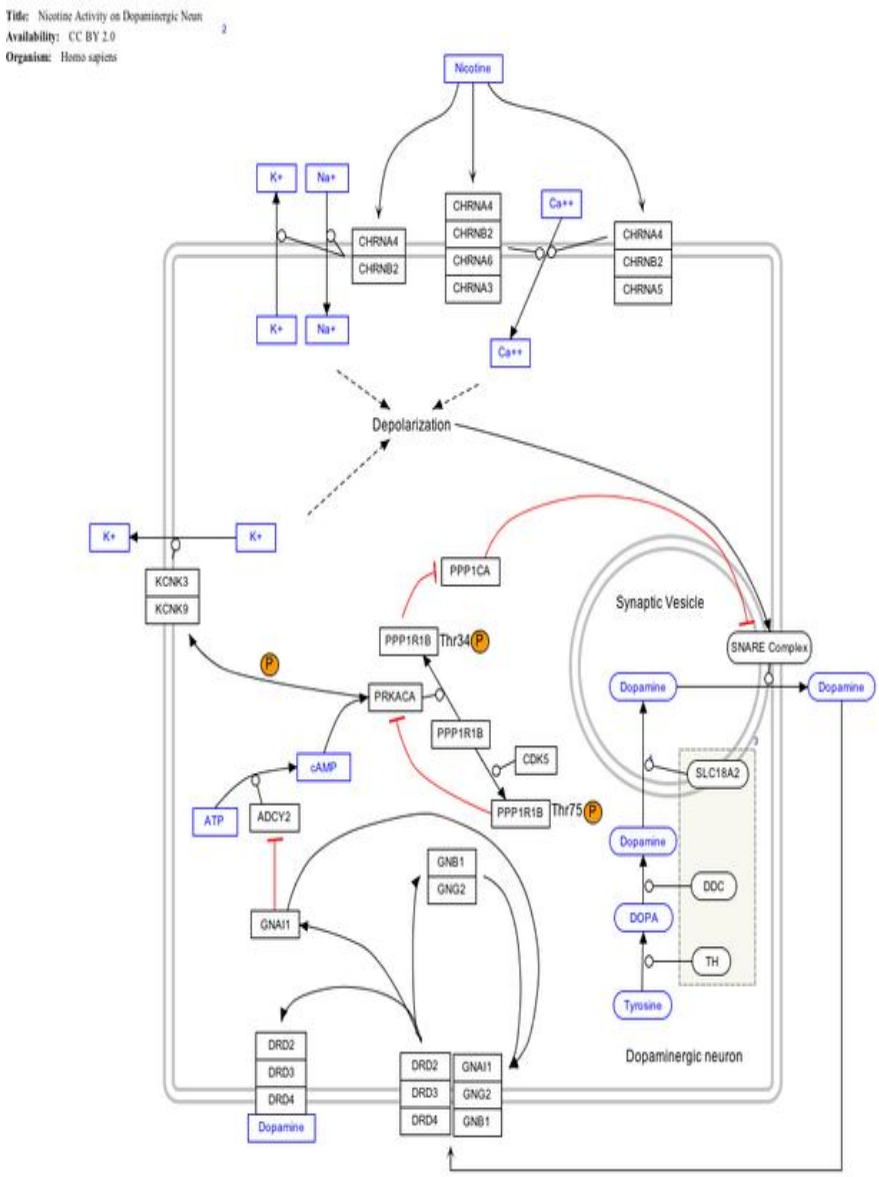
Mechanism of action:

Central nervous system :

Nicotine acts on the receptors of the central nervous system. They are anticholinergic by action. It also activates the release of other neuro transmitters like dopamine. This mechanism is responsible for the euphoria caused by nicotine.

Cigarette smoking and atherosclerosis. The release of dopamine is through cholinergic pathways. The

activation of cholingergic receptors in the central nervous system is more than the skeletal system. Nicotine also contains inhibitors of the enzyme mono amino oxidase[34]. Dopamine , serotonin and epinephrine are mainly metabolized by this enzyme. This leads to increase in half life of dopamine. This leads to prolonged euphoric effect of nicotine.



Sympathetic nervous system:

Nicotine also has its action on sympathetic nervous system. It causes the release of

Acetyl choline from preganglionic fibres. This acts on the adrenal medulla which is the largest ganglia. Epinephrine is released from adrenal medulla into blood. This acts on various organ systems leading to increased heart rate ,

increased blood pressure and higher blood glucose. Acetyl choline released by nicotine causes the entry of calcium inside the chromaffin cells. This leads to the release of epinephrine from the cells of adrenal medulla. This process is called as exocytosis[35].

Toxicology:

The lethal dose of nicotine in humans is found to be 50 mg[36]. The range varies from 30 to 60 mgs.caffiene is also an alkaloid. But compared to caffeine, nicotine is very toxic as the lethal dose is very small. Nicotine promotes the formation of cancers in various aspects. It

1. Increases the production of growth factors.
2. Inhibits the apoptosis of the cells by continuous stimulation of cell cycle by sympathetic pathway.
3. It also promotes the vascularisation of tumour cells.

In pregnant woman nicotine adversely affects the fetus. It causes the vasospasm of umbilical arteries. This leads to poor perfusion of fetus. As a result the growth of brain of

fetus is affected. Brain metabolism is also affected. These manifests as poor neuro behavior of the newborn.

Nicotine exerts its action in the brain through dopamine. When the smoking habit is suddenly stopped the levels of dopamine in the brain decreases. As a result the dopamine receptors and oversynthesised to counteract the deficiency of dopamine. This leads to increased sensitivity of dopamine receptors to dopamine in the brain.

Detection of use:

Serum levels of the nicotine levels are important in a medico legal investigation. But serum levels of the nicotine increases in persons who are exposed to passive smoke.

Health effects of nicotine:

The health effects achieved through smoking are called as smokers paradox[37]. The mechanism of action for such paradox are poorly understood. After detailed researches they found out that it is due to the substance nicotine.

Nicotine whether consumed by a person either in the form of smoke or patches have the same effect.

Smoking offers a beneficial role in a variety of diseases. These include

1. Ulcerative colitis
2. Allergic asthma
3. Pre eclampsia[38]
4. Atopic disorders
5. Kaposi sarcoma

Nicotine present in the smoke is a vasoconstrictive substance. In inflammation there is release of cytokines leading to vasodilatation. But due to nicotine the vasodilatory effects of the inflammation are prevented. Thus nicotine is very useful in many inflammatory diseases and diseases where vasodilatation is the main pathogenic factor.smoking is also very useful in the treatment of major depressive disorders. Smoking increases the risk of alzheimers disease where as the nicotine present in the smoke reduces the formation of alzheimers disease[39]. Smoking is also tried in the

treatment of obsessive and compulsive disorder and the results are successful in small scales. Smoking decreases the risk of ulcerative colitis but the risk of developing crohn's disease is increased.

Psycho active effects:

Nicotine has two main psycho active effects. They are

1. Stimulant effect
2. Relaxant effect[40]

These effects are mainly due to the release of neuro transmitters in the brain. They are also due to the release of glucose from liver and also release of adrenaline from the adrenal cortex. Smoking is also associated with reduced appetite. This leads to loss of weight in smokers. The time taken for nicotine to reach the brain from lungs to brain is just seven seconds. Once it reaches the brain it causes the release of various neurotransmitters. They include mainly epinephrine , acetyl choline and norepinephrine. The other important ones are dopamine and serotonin. Endorphins also play a role in the stimulant effect.

Alertness and arousal are caused by norepinephrine. Concenteration is increased by nicotine. Memory is thought to be increased by acetyl choline. Relaxation is mainly mediated by serotonin. When the smokers inhale short puffs the effect achieved is stimulation. This is due to the release of dopamine in the nerve terminals of the central nervous system. When the subjects take deep puff the effect achieved is relaxation. This is mainly due to the release of the serotonin released in the nerve terminals of the central nervous system.

Nicotine – an insecticide:

During the period of world war II nicotine is mainly used as an insecticide. After the world war was over the usage of nicotine as an insectide has been drastically reduced. This is mainly due to the synthesis of the insecticides that have reduced toxic effects to the humans and animals.

History of smoking:

The habit of smoking was first discovered by the people of America . they were called as native Americans.they

smoked during ceremony. They also thought that smoking had medicinal purposes. Coloumbus then brought the leaves of tobacco to Europe. Europeans had their habit of smoking from the middle of sixteenth century. Nicotine was discovered by jean nicot. The drug was given its name after the scientist. Smoking began a common recreational practice in france then in Portugal. The cultivation of tobacco first began in the united states of America as a cash crop. This was done by john rolfe in 1612. Within few years it became the main export business of America. Initially tobacco was used in the form of cigars. They are also chewed. Cigars were not popular during the initial period. Cigarettes were very popular since 19th century. Cigarette smoking was initially considered to be a positive habit. Even many physicians prescribed smoking as a good medicine. The negative aspects of smoking came to light only after 20th century.during the year 1930 it was found that smokers can't live as long as non smokers. Many researches were done on this. Cancer society of Aerica has found that

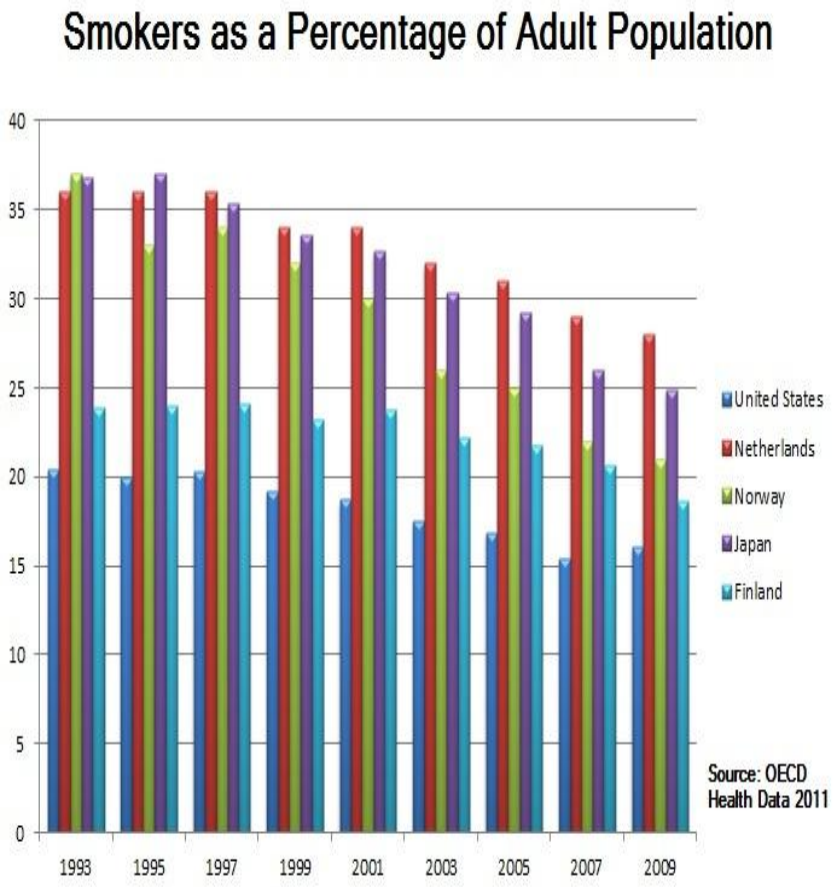
smoking can lead to many cancers. But there is evidence to prove this. The causal relationship between smoking and cancer could not be established . The uneducated people could not understand the statistical researches. Tobacco research council was established and it published the adverse effect of smoking. Low tar cigarettes were introduced then and the sales increased then. The causal relationship between smoking and cancer was established in 1964. It was concluded that smokers are at a high risk of developing lung cancer than the nonsmokers. Similar results were esbablished in females too. Some of the substances were specifically found to be carcinogens in smoking . these include arsenic and cadmium. General warning on the labels of cigarette packs were introduced since 1964. Advertisement of cigarettes were stopped since 1971. The habit of smoking in flights were stopped since 1990. Orders were given to FDA to regulate the sales of cigarettes to minors.

Smoking in india:

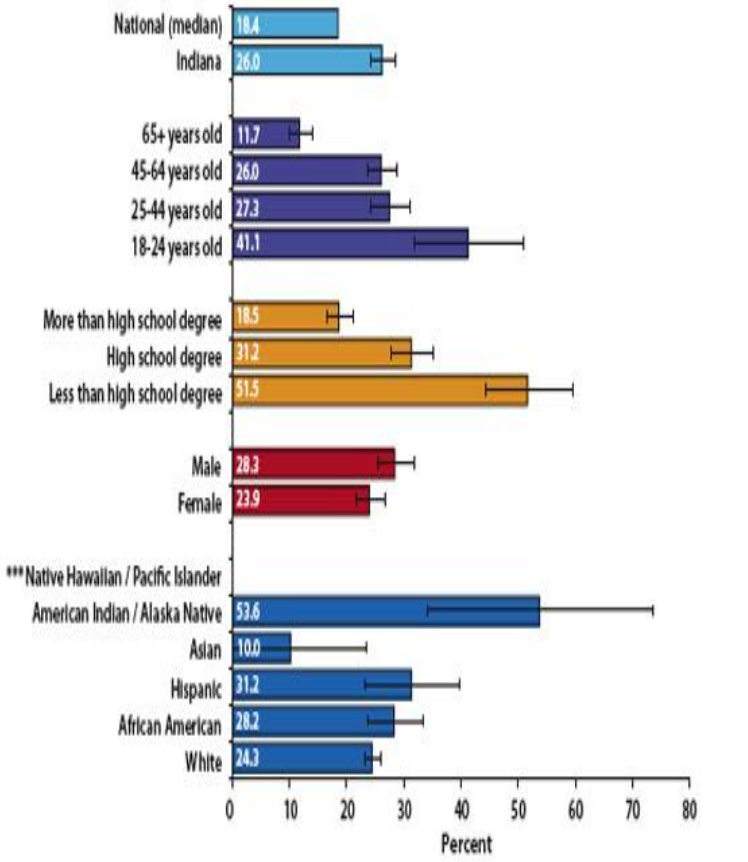
Smoking in india was described since 2000 BC. Cannabis smoking was practiced since before Christ . initially smoking was done in the form of fumigation. Smoking was also practiced in the form of Homa. In this method various substances were put into fire including milk , fish and skin of snakes. Initially smoking was practiced as a form of medicine in ayurvedha . tobacco smoking in india was introduce in 17^{th} century. Since then it merged with old practice of smoking. Smoking in public places was prohibited since November 2001. Smoking ipracticed by 12 crore people in india. This contributes to 12% of the total smokers in the world. About thirty percent of the Indian males smoke. More than nine lakh smokers in india die every year. Females also smoke in india. But the proportion is very less. It is about 2 to 4%. Cigarette smoking is highly practiced in the state of jammu and Kashmir. Beedi smoking is more in the state of uttarkhand. Statuatory warning in the packs of cigarettes were introduced in the year of 1975 by the

supreme court of india. Smoking within 100 yards from educational places were introduced since December 1 2004. In india Chandigarh is called as the smoke free city. Similarly shimla is trying to be the second smoke free city. Smoking in public places has been banned from October 2008. This includes places like cinema theatres , pubs, bars ,temples , public transport places like bus stand , railway station , airports and harbours. Pictorial warning on the cigarette pack was introduced in may 13 2009. This involves a demonstration of a picture showing the adverse effects of smoking. Video advertisement showing the harmful effects of smoking were introduced since October 2nd 2012. These were shown before the

start of the movie and during intervals.

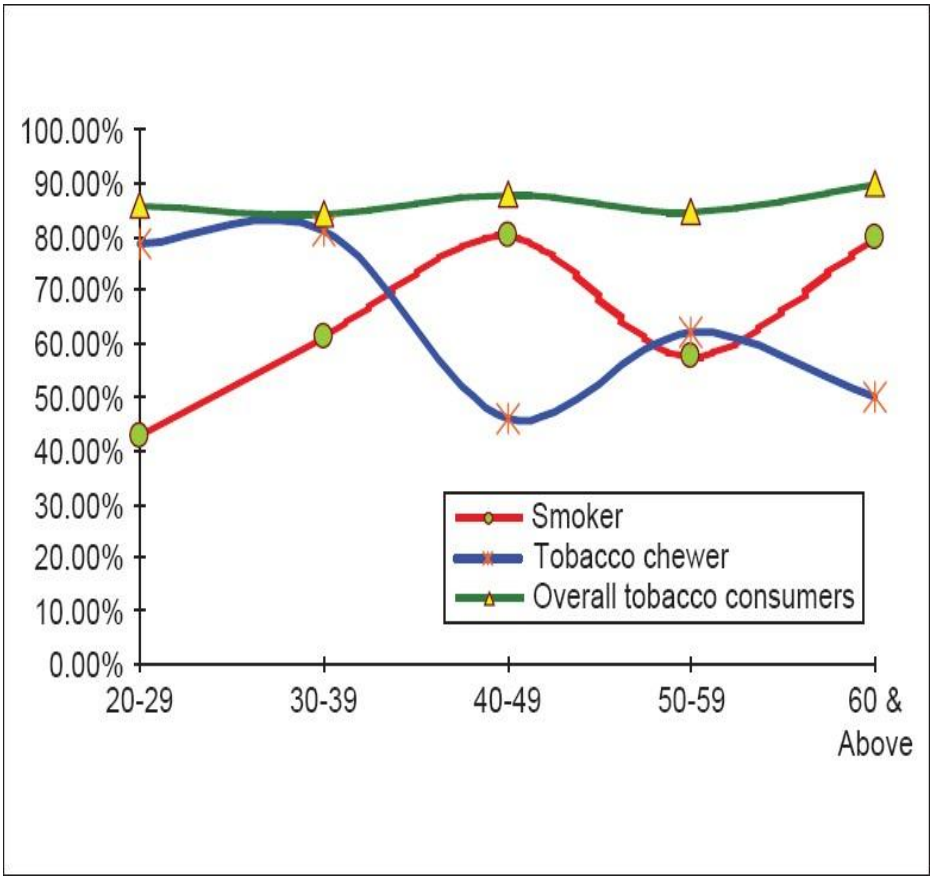


Current Smoking among Adults by Demographic Characteristics



*** Data not shown because sample size is less than 50.

Source: BRFSS, 2007-2008



MAJOR ADVERSE EFFECTS OF SMOKING:

Smoking is responsible for many adverse effects out of which the following four are more important.

1. Cancer
2. Non cancerous lung diseases
3. Atherosclerotic diseases of aorta and coronary blood vessels.
4. Toxicity to reproductive system

The most important ingredient of smoking is nicotine. It is a psychoactive drug

which is responsible for craving during the time when a person makes an attempt

to stop smoking.

Cancer:

Smoking is responsible for the following cancers.

1. Lung
2. Oesophagus
3. Oral cavity
4. Larynx
5. Bladder
6. Pancreas.

The most common cancer associated with smoking is lung cancer.

The risk of developing cancer depends on

- the number of cigarettes smoked daily
- the duration of smoking
- active or passive smoking
- age at the onset of smoking
- factors associated with smoking like

1. Alcohol

2. Radiation exposure

3. Asbestos

4. Certain Viral infections.

The main carcinogenic effects of smoking is attributed to

1. Mutation

2. DNA damage.

These two process leads to malignant transformation of mammalian cells into

malignant cells.

When condensed cigarette concentrates are applied to the shaved skin of mice

most of the mice developed skin cancers.

Each puff contains about 30 to 70 ml of smoke. The main chemical ingredients are

1. Benzo(a)pyrene (bap) such as dibenzo-acridine\

2. N-nitrosamines such as NDMA

3. Aromatic amines such as 4-aminobiphenyl

4. Aldehydes such as formaldehyde

5. Organics such as benzene

6. Inorganic compounds such as arsenic, nickel, and chromium.

These substances can induce tumours by either acting as an

1. Initiators : initiating tumour development

2. Promoters: cant initiate but promote the development of previously initiated

cancers.

Certain substances in smoke are known to produce specific tumours.

They are

I. TNSA:

It produces cancers of

a. Lung

b. Larynx

c. Oesophagus

d. Pancreas

II. Aryl amines:

It produces cancer of bladder.

III. Benzene:

It produces leukemia.

NON CANCEROUS LUNG DISEASES:

The main non cancerous lung disease produced by

smoking is chronic obstructive lung disease. This occurs after repeated injury to lung tissue by smoke. During the early years of smoking there is no symptoms experienced by smokers but pulmonary function tests revealed abnormalities. There is a dose dependent change in pulmonary function tests and the duration of smoking concluded by many studies. Over a period of 2 decades or more chronic obstructive lung changes begins to appear. This includes

1. Mucous hypersecretion leading to cough with expectoration
2. Airway thickening and inflammation of small airways
3. Emphysema : abnormal dilatation of terminal airways with

thinning of airways causing obstruction of airways during expiration.

As a result of these changes life style of smokers begins to change leading to morbidity.Each person develops any type of changes described in the above spectrum.

Some persons will have more cough with expectoration while some others develop airway obstruction features. At

the endstage all persons will have features of all the 3stages of spectrum..The mechanisms by which smoking produces changes in respiratory tracts includes

1. Toxicity to cilia:

Cilia along with the mucous secreted by respiratory epithelium is responsible for propelling the foreign body that enters the respiratory tract. By damaging cilia smoking causes stagnation of mucous in respiratory tract . this leads to the growth of pathogenic organism in the mucous plug leading to the damage of the walls of the respiratory tract leading to abnormal and irreversible dilation of the small sized bronchioles.

2. Inflammation:

Smoking also causes damage to respiratory tract by inflammation of the airways. The main mechanism by which smoking promotes inflammation is by means of the oxidative substances present in it. Smoke contains an enzyme called as elastase which breaksdown the elastic material present in the walls of lumen. Smoke also inhibits alpha 1 antitrypsin a substance which inhibits the

enzyme elastase thus promoting the destruction of airways. Smoke contains many other volatile and non volatile substances which damages the respiratory tract .these include

- Hydrocarbons
- Aldehydes
- Ketones
- organic acids
- Phenols
- Cyanides
- Acrolein
- nitrogen oxides.

Some agents are concerned with the production of excessive mucous production while some others are concerned with small airway abnormalities while the rest are associated with emphysematous changes.

Atherosclerotic heart disease:

Smoking is associated with the formation of atherosclerotic plaque formation and its subsequent rupture and formation of thrombosis. This occurs in any

of the main vessels like coronary circulation , cerebral vascular tree , aorta and in limb vessels.The main site of atherogenesis is coronary circulation which may present in the form of stable or unstable angina , heart failure , sudden death. If it occurs in cerebral circulation this is called as stroke . when this occurs in limb vessels as peripheral vascular disease. The process by which smoking promotes atherogenesis are

1. Reducing the value of HDL cholesterol.
2. Increasing the value of LDL cholesterol.
3. Increasing the oxidation of LDL cholesterol.
4. Promoting the entry of LDL cholesterol in endothelium.
5. Increasing the adherence of platlets to endothelium.
6. Increasing the formation of blood clot thereby occluding the already narrowed vessel.

The substances which promotes the formation of atherogenesis are

1. Nicotine:

Nicotine increases the heart rate and circulation. It also causes injury to the endothelial lining .

2. Carbon monoxide:

It binds with hemoglobin and reduces the oxygen carrying capacity of cells and keeps the myocardium in the state of hypoxia.

3. Polycyclic aromatic hydrocarbons:

4. Free oxygen radicles:

It damages the endothelium and promotes the formation of atherosclerosis.

Cigarette smoking and reproduction:

Smoking affects reproduction in both sexes. In males it causes impotence. The cause of impotence may be due to the vascular disease affecting the vessels supplying the genitalia. In females it causes infertility. This may be due to reduced motility of the eggs in fallopian tubes or it may be due to recurrent infections of the fallopian tubes due to suppression of immunity by smoking.

Cigarette smoking affects the maternal and fetal outcome.

It causes

1. Spontaneous abortion

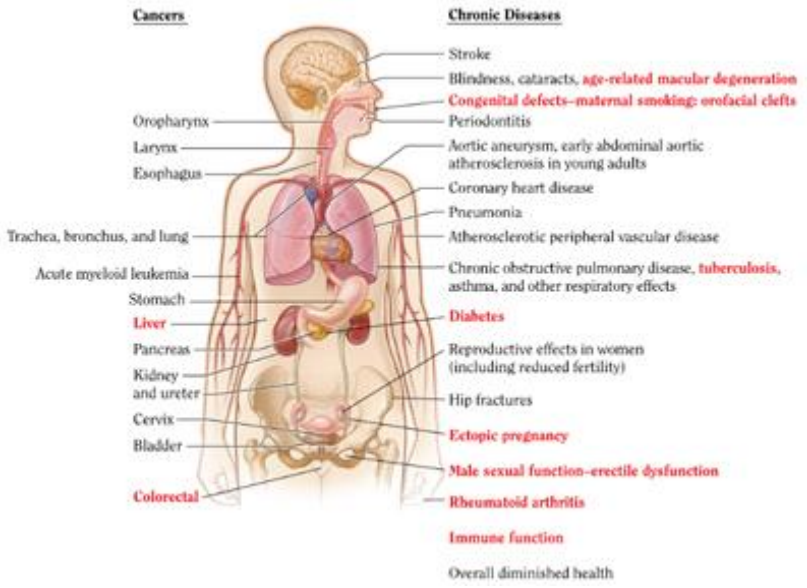
2. Low birth weight

3. Preterm delivery

4. Bleeding during pregnancy.

Nicotine is the main substance causing all these problems.

Poor weight gain During pregnancy due to smoking is also the mechanism for low birth weight. Smoking also causes vasospasm of the umbilical arteries . carbon monoxide present in the smoke can cross the placenta and binds with fetal hemoglobin and causes poor oxygen delivery. Smoke contains cyanide which also causes harmful effects. Smoking women experience early menopause compared to non smokers while heavy smoking women have early menopause compared to light smoking women..



Smoking also associated with development of rheumatoid arthritis.Smokers have a very high risk of developing diabetes mellitus compared to non smokersSmokers have reduced bone mineral density leading to the development of osteoporosis and also early tooth lossSmoking is also associated with the early onset of cataracts and also age related macular degeneration.

Comparison of type of smoking:

Smoking may be in the form of cigars , beedis and cigarettes. Nothing is safer than other in causing adverse effects. Similarly menthol coated cigarettes have no advantage over other cigarettes in fact they are more worse than normal cigarettes.Since they have cooling effect they suppress cough reflex and make the person to take more and more puffs. Smoking even as low as 1 cigarette per day is associated with definite cardio vascular risks. Similarly e – cigarettes are also not safer than normal cigarettes . their ingredient is not known. They also contain nicotine which leads to addiction.

Smoked tobacco in India

Beedis:

Beedis are substances which is made of dried tobacco wrapped inside an rolled to form a beedi[41]. Beedis are smaller in size when compared to the cigarettes as a result of which people smoke more beedi to attain the satisfaction produced by nicotine. Beedi rolling serves as a major source of income in running familes in many villages of India.The effects of both smoking

cigarettes and inhalation of tobacco flakes is similar.Hence there is an increase in the risk of cancers specifically lung cancer to the members of the family.

Cigars and Cigarettes:

Cigars-These are nothing but a wrap of tobacco leaf inside which dried tobacco is filled.

Cigarette-Here the roll of tobacco instead of the leaf is wrapped in a Paper[42].Cigarettes in the market come with a lot of variety for example: with filters,low tar,menthol and even flavoured ones which makes the customers fall for and producing a misconception that cigarette smoking thus causes less harm to our health.People belive that cigars are smaller in size and causes less harm but are unaware that a large cigar can contain so much tobacco so it becomes equal to one whole packet of cigarette. Smoking cigarette is on an alarming rise and is becoming common even among teenage girls and young women.

Chilum:

In this type tobacco is smoked in a clay pipe.This type poses the person to an increased risk of oral cancer and lung cancer.A group of people share a chillum and hence

apart from increasing the risk of oral cancer it also makes them vulnerable for cold and other respiratory illnesses.

Hookah:

This is also an unsafe way of smoking and the mechanism is the tobacco is heated by a device and before the smoke is inhaled it passes through water.Though this type of smoking was declining for a period it is now again on the rise.It is available in flavors like apple, chocolate.etc in coffe shops as they depict a sign of royalty and prestige.This pattern of smoking which inclines the person more towards addiction is used more commonlamong the college boys and girls.

Chutta smoking and reverse chutta smoking:

These are smoked in the coastal areas of India and are nothing but coarse tobacco cigars.

Reverse Chutta smoking:

In this method the burning end of chutta is kept in the mouth and the smoke is inhaled.This has the highest risk of oral cancer

REVIEW OF LITERATURE

1.RELATIONSHIP OF CIGARETTE SMOKING AND SNUFF DIPPING TO PLASMA FIBRINOGEN,FIBRINOLYTIC VARIABLES AND SERUM INSULIN – THE NORTHERN SWEDEN MONICA STUDY

This study consisted a randomly selected population consisting of 604 males and 662 females between the age 25 and 64 years.They were grouped as regular smokers(>1cigarette /day),ex-smokers,snuff dippers and non -tobacco users.Men who smoked had 0.34g/l(95% CI 0.17to 0.49) higher fibrinogen level than non tobacco users.The number of cigarettes smoked correlated with plasma fibrinogen levels.Female smokers had significantly higher fibrinogen levels than ex-smokers .The Difference when compared with non smokers was not that significant.

Conclusion: cigarette smoking is associated with

- Higher fibrinogen levels
- Normal glucose tolerance and insulin levels
- Unaltered fibrinolysis

- Use of smokeless tobacco as moist oral snuff,does not appear to affect these potential cardiovascular risk factors.

2.ANNALS OF EPIDEMIOLOGY,MAY 2001,ORIGINAL REPORT – SMOKING,OTHER RISK FACTORS AND FIBRINOGEN LEVELS EVIDENCE OF EFFECT MODIFICATION

Purpose- This study aims at denoting that smoking modifies the association between the traditional risk factors of early atherosclerosis such as dyslipidemia, hypertension,or diabetes mellitus,with fibrinogen a risk factor more closely associated to plaque progression and thrombosis.

Methods- the sample for this study was collected from the MONICA Augsburgpopulation survey of 1989/90 which included 1840 men and 1784 women aged between 25 to 65 years. Plasma fibrinogen concentration was determined by nephelometry.

Results-

- Fibrinogen levels were higher in women than in men and higher insmokers than in non smokers.

- The effect of smoking was greater in men.The elevation of meanadjusted fibrinogen levels in men was significantly higher in smokers than in non smokers.

- By contrast smoking in women showed significantly stronger impacts only with regard to the association of dyslipidemia and fibrinogen.

Conclusion

Smoking contributes more than additively to the strong influences od risk factors on fibrinogen levels.These data confirm that smoking is a dominant determinant of fibrinogen levels.

3.EFFECTS OF SMOKING AND ABSTENTION FROM SMOKING ON FIBRINOGEN SYNTHESIS IN HUMANS:

The significant risk factors for development of cardiovascular disease are both smoking and hyperfibrinogenemia.Two studies described aims to establish the mechanism responsible for raised plasma fibrinogen concentration seen in smokers.

The **absolute rate of fibrinogen synthesis(ASR)** was **increased** in **smokers** than non smokers and the plasmalevel of fibrinogen correlates significantly with fibrinogen synthesis.On the contrary plasma albumin

concentrations were low in smokers than non smokers with no difference in the rates of albumin synthesis between the two groups.There was marked fall in plasma fibrinogen concentration and a significant reduction in ASR in previously chronic smokers who stopped smoking for 2 weeks.

Large scale studies have consistently demonstrated that an increased plasma fibrinogen concentration is an independent risk factor for a cardiovascular event for which the Northwick park heart study is a goodexample.Cigarette smokers is a group of population which consistently exibhits increased incidence of vascular problems.Cigarette smoking is a independent risk factor for stroke and ischaemic vascular disease and also doubles the fatalities from coronary heart disease.The most common aberration of the hemostatic system found in smokers is raised plasma fibrinogen concentration and the clinical significance has been highlighted by several inveatigators.Kannel et al for example used data from the Framingham study to estimate that 50% of smoking associated with ischaemic heart disease may be mediated through the deleterious effects of fibrinogen.Though attention has been focussed on the

relationship between smoking and increased plasma fibrinogen level the mechanism has not been elucidated.

This paper described two studies which used **isotope methodology** to Perform in-vivo investigations to know about the influence of cigarette smoking on fibrinogen synthesis.

In the first study the rates of fibrinogen synthesis was compared in groups of smokers and non-smokers. Whereas in the second study a group of chronic smokers who were abstained from smoking for 14days were chosen to determine if short term cessation affected fibrinogen synthesis.Through this study it was also possible to investigate the synthesis of albumin in smokers.

Methods

All the participants were healthy and medication free.exclusion criteria included diabetes,overt liver,kidney or thyroid dysfunction,infection,routine consumption of aspirin,lipid lowering or fibrinolytic drugs,a history of vascular disorders,obesity,hypertension and hyperlipidemia. Since an acute phase response alters fibrinogen metabolism participants with plasma

concentrations of C-reactive protein >10mg/l were excluded.All measurements were performed after patients fasted for 12 hrs.Since variables like age, sex and body mass index were thought to influence plasma fibrinogen concentration for study 1 these particulars was matched between eight male smokers and non smokers. To standardize smokers were asked to retain smoking 1hr before the measurements were made.

For study 2 eleven male chronic smokers within the specific criteria were recruited. Measurements were performed before and immediately after a 2 week period of complete abstention from smoking.Participants were asked to refrain from smoking for 9 hrs.Urinary concentration of cotinine which is ametaboliote of nicotine was measured on two occasions during smoking abstinence to monitor the compliance to non smoking. Urinary cotinine levelswere compared with a reference range obtained from a group of non-smokers. Participants whose urinary continence level exceeded the maximum value of this range(55µg/ml) were excluded from the study.

Measurement of the rate of fibrinogen synthesis

The rate of fibrinogen synthesis was measured according to the methods of balmer et al following injection of a specific type of phenyl alanine.The blood samples were then taken at specific times to know the isotopic enrichment of the plasma free amino acid and newly synthesised protein.

The rates of fibrinogen synthesis was expressed as both as fractional and absolute rates.(FSR and ASR). Plasma fibrinogen and serum C-reactive protein concentraions were measured immunologically by automated –laser rate nephelometry.

Results

Study 1-

- **The plasma fibrinogen concentration** was on an **average 10%higher in smokers** than the non-smokers but did not show muchstatistical significance.
- The rate of fibrinogen synthesis expressed as percentage of **plasma fibrinogen pool was higher in smokers** than non-smokers which was also not statistically significant.
- The **absolute rate of fibrinogen synthesis**, i.e. the

amount of fibrinogen synthesised by the liver per day was **significantly greater in smokers** when compared with the non-smokers. Smokers also had significantly lower plasma albumin concentrations when compared with the non-smokers.

Study 2-

Eight of the eleven male participants hasd successfully completed the study.The others were excluded due to development respiratory infection and elevated urinary cotinine levels.The mean urinary cotinine levels of the successful abstainers was 0.20±0.03µg/ml,which suggested they had compiled with the non-smoking regimen.The increase in weight seen in smokers who had abstained from somking was significant to the present study because it resulted in increased estimated plasma volumes for use in the calculation of fibrinogen ASR.

- A **fall in plasma fibrinogen concentration** was observed in all the participants(smokers) as they had **abstained from smoking** as per the protocol, an average

reduction of 19%.

- The **average decrease of FSR was 14%** due to cessation from smoking.
- The average reduction in fibrinogen ASR was 33% following smoking cessation.

Discussion

The major risk factor for developing cardiovasculardisorders is hyperfibrinogenemia bypromoting a multitude of atherogenic and thrombogenic processes,which is thought to be as important as raised plasma cholesterol.The mechanisms by which fibrinogen and its derivatives are thought to accelerate athero thrombogenesis include :

- Stimulation af vasoactivity
- Alteration of prostaglandin metabolism and tissue oxygenation
- Promotion of platelet hyperactivity and erythrocyte aggeregability
- Initiation and sustained growth of atherosclerotic lesions.

As a consequence ,researchers recommend that plasma fibrinogen should be included during the assessment of cardiovascular risk. **The stongest known environmental influence on plasma fibrinogen concentration is smoking and has consistently been linked to the development of elevated plasma fibrinogen.**Conversely,cessation from smoking results in a rapid reduction in plasma fibrinogen which subsequently may reamin elevated for several years.This paper aimed to establish if the hyperfibrinogenemia in smokers is accompanied by an increased rate of synthesis and, conversely, whether synthesis is reduced by short-term smoking cessation. Thus the result i.e**. higher plasma fibrinogen concentrations ofsmokers compared with non-smokers and the significant fall in plasma fibrinogen concentration with two weeks abstention from smoking** are inaccordance with the previous study.The elevated levels of plasma fibrinogen concentration in smokers also correlated with elevated levels of fibrinogen synthesis.The rates of fibrinogen synthesis were reduced to levels comparable with those of non-smokers after abstention .These results from both studies support the proposal that smoking induces

fibrinogen synthesis and this effect can be reduced by abstention from smoking.The rate of synthesis of fibrinogen and the rate of removal of fibrinogen from the plasma determines the fibrinogen concentration in the plasma.It is clear from the studies that the rate of synthesis of fibrinogen is increased in smokers but the rate of removal could not be measured.The magnitude of changes in the ASR were greater than the observed differences in plasma fibrinogen concentration between smokers and non-smokers or absatiners ,suggesting that the rate of disappearance of fibrinogen from the plasma was also elevated in smokers when compared with non-smokers or abstainers.The difference in the fibrinogen ASR of smokers and non-smokers(study1) andthe reduction in fibrinogen synthesis which occurs from abstention from smoking(study2) are due to several biochemical mediators.Chronic smokers exibhit a mild,but sustained acute phase response,characterised by increased plasma concentrations of positive acute phase proteins such as fibrinogen and alpha-1-antitrypsin.Tobacco smoke inhalation causes a persisting inflammatory insult to the cells which is the reason for this response.The increase in plasma concentration of

fibrinogen during the response is attributed to increased fibrinogen synthesis via a stimulation of transcriptional activity.Cytokines are thought to be the important mediators of this response of which specifically interleukin-6 may be the reason behind the enhanced rate of fibrinogen production in smokers.In smokers the plasma concentration of interleukin-6 has found to be

elevated. Cathecholamines may also be mediators of the smoking effect on fibrinogen synthesis in addition to cytokines.Cathecholamine release is stimulated by smoking and studies have demonstrated that epinephrine increases fibrinogen synthesis directly possibly by enhancing m-RNA synthesis. Since incubation of human liver slices with fatty acids accelerates incorporation of amino acids into fibrinogen and plasma non-esterified fatty acid concentrations are elevated after smoking it is suggested that fatty acids may also have a role in enhancing the fibrinogen production in smokers. The above said mechanism is facilitated by thrombin. This is proved as the injection of thrombin into mice has resulted in non-esterified fatty acid concentrations and a stimulation of fibrinogen production and thrombin

generation is induced by smoking.

Conclusion-

- The increase in the rate of fibrinogen synthesis seen in chronicsmokers is atleast partially responsible for the hyperfibrinogenemia.
- Short term cessation from smoking results in significant reduction in the rate of fibrinogen synthesis.

4.SMOKING CESSATION AND CARDIOVASCULAR DISEASE RISK FACTORS:RESULTS FROM THIRD NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY

Background

Smoking is considered to be the important risk factor not only for development but also for the progression of cardiovascular events.The high levels of inflammatory markers and atherosclerosis is attributed to smoking. The impact of smoking cessation on levels of inflammatory markers have been widely examined by various studies.The degree and rate at which inflammation decreases after smoking cessation is not clear.

A total of 15489 individuals participated in

the Third National health and Nutrition Examination Survey(NHANES III).From this study the association between smoking and and smoking cessation on levels of inflammatory markers and traditional cardiovascular risk factors was analysed.Of the inflammatory markers in particular changes in C-reactive protein, fibrinogen, albumin, white blood cell count were examined. A temporal and dose dependent relationship was demonstrated between the inflammatory markers to smoking and smoking cessation. The inflammatory and traditional risk factors improved with decreased intensity of smoking. Moreover inflammatory markers resolved more slowly than traditional cardiovascular risk factors with increase in time since smoking cessation.

Introduction- Through several pathways in both a duration and dose dependent manner smoking accelerates atherogenic cardiovascular disease.

Smoking incites:

- Endothelial cell dysfunction
- Foam cell proliferation in tunica media
- Enhances platelet aggregation

- An immunologic response to vascular injury
- Depresses high-density lipo-protein(HDL)cholesterol
- Oxidative stress leading to lipid peroxidation
- Impairs lipoprotein metabolism

There is a significant increase in C-reactive protein, white blood cell count, fibrinogen whereas decrease in serum albumin during the acute phase of inflammatory states. With regard to the future cardiovascular events the acute inflammatory markers have found to be both predictive and prognostic. The most important inflammatory marker in the process of atherosclerosis is C-reactive protein. It has been found that CRP is also produced at the site of atherosclerosis by smooth muscle cells. C-reactive protein in the vessel wall induces expression of adhesion molecules on endothelial cells. Thus increases monocyte chemotactic protein-1 which inturn attracts the monocytes and T cells into the vessel wall.C-reactive protein is also a mediator in the pathogenesis of atherosclerotic cardiovascular disease.

From the Third national Health and Nutrition Examination Survey(NHANES III)the association

between smoking and smoking cessation and the levels of inflammatory markers and traditional risk factors was tested.The association between decreased smoking and increased time since smoking cessation to changes in the inflammatory markers – C-reactive protein, fibrinogen, albumin, white blood cell count and the traditional risk factors-total cholesterol, triglycerides, HDL cholesterol, systolic blood pressure.

The primary aims are:

- To denote the excess cardiovascular risk associated with smoking and any associated decline in risk with smoking cessation by investigating changes in C-reactive protein.
- Whether the inflammatory markers observed cardiac risk reduction following smoking cessation from smoking.

Methods-

Study population-NHANES III was a study conducted between 1988 and 1994.The NHANES III population included 19,618 persons some were excluded due to various reasons and data for 15,489 persons were

analysed. Several clinical factors were analysed based on self reporting by the participants, questionnaires and clinical examination. Investigations were taken for dieases like diabetes mellitus, hypertension with specific cut-off values. Serum cholesterol and triglyceride values were measured enzymatically. More importantly, based on both self-reporting and serum cotinine levels the study population was classified.Persons with serum cotinine levels more than 56.8nmol/land those who gave a history of current smoking were consideredcurrent smokers.This group was in turn divided into four roughly equal groups based on number of cigarettes smoked per day: 1-9,10-19,20-29 and more than 30 cigarettes per day.Former smokers were classified by years sincesmoking cessation: <1, 1-3, 3-5, 5-7, 7-9 and >9 years since smoking cessation.Those with serum cotinine levels less than 56.8nmol/l were denoted as never smokers.Smokers at the lowest dose intensity level were those Passive smokers with cotinine levels over 56.8nmol/l.

Nephelometer was used for measuring C-reactive protein.Fibrinogen was measured using a quantitative assay of clotting time. Mantel tests for trend

was used for knowing the relationship between both time since smoking cessation and smoking intensity and the assessment of each of the outcomes.

Three sets of tests were performed:

- by cigarettes per day among current smokers
- by time since cessation among former smokers
- despite the potential nonlinearity between the groups among smokers, former smokers and non-smokers .

Results

Total sample consisted of 15489 persons of which 3459 were classified as former smokers 7665 were classified as never smokers and 4365 as current smokers. The average time since smoking cessation for former smokers was 13 years. The average cotinine level for current smokers was 1255 nmol/l;for both former and never smokers the average cotinine level was <3nmol/l.

Among the inflammatory risk factors, analysis of smoking status in a bivariate way showed that unadjusted C-reactive protein, fibrinogen and white blood cell count were all well increased. Smokers also had higher total cholesterol antriglycerides.Prevalent

atherosclerotic cardiovascular disease was seen in former smokers. C-reactive protein had a co-relation with older age, female sex and black race. Similarly significant associations were observed in serum albumin and serum fibrinogen.

The reduction of inflammatory response was observed

- With reduction in the smoking intensity
- Increased time since the person has stopped smoking

C-reactive protein and fibrinogen were higher with increased smoking intensity and were all negatively associated with time since the person quit smoking.The traditional cardiovascular risk factors such a s total and HDL cholesterol,triglycerides,alcohol usage and systolic blood pressure showed a dose-dependent association with smoking intensity.

Among the inflammatory markers C-reactive protein continued to show reduction of acute phase reponse with a decrease in smoking intensity and increased time since cessation.

Overall the following associations were made:

- Positive changes in both inflammatory markers and traditional risk factors

with decreased intensity of smoking and

- with increased time since cessation from smoking there is improvement in

inflammatory markers.

Discussion-It is known that after 5years of cessation from smoking the

inflammatory changes reduces. With reduced exposure to tobacco vascular

effects can be reversed and cardiovascular risk reduces gradually.

These studies have examined inflammatory markers following

smoking: the MONICA Study (Monitoring Trends and Determinants in

cardiovascular Disease), Northwick Park Heart Study and the Cardiovascular

Heart Study(CHS). The Northwick Park Heart study and MONICA study both

found that fibrinogen levels reached normal levels within 5years.

Tobacco ranks the second important cause of preventable death in the world.It

is also the fourth most common risk factor for disease.

Conclusion-Thus this study suggests that inflammatory problems

of the cardiovascular disease that results from smoking is reversible with

cessation of smoking.

MATERIALS AND METHODS

MATERIALS AND METHODS

This study was conducted in our medical college hospital. Patients recruited from medicals wards and IMCU. A total of about 160 patients were selected and 10 of them were excluded as per exclusion criteria used. The remaining 150 patients were included in the study.Among them 100 patients are smokers and 50 are nonsmokers Informed consent was obtained from all patients. Serum fibrinogen value was estimated in all 150 patients admitted in our hospital.

INCLUSION CRITERIA

1. Patients and Relatives of outpatients and inpatients in tirunelveli medical college.
2. Healthy individuals between 20 to 60 years of age.

EXCLUSION CITERIA

1. Patients with history of diabetes mellitus
2. Patients with history of hypertension
3. Patients having hyperlipidemia
4. Patients having vascular disorder,

5. Patients having liver , kidney dysfunction
6. Patients having thyroid dysfunction
7. Patients having Infection,
8. Patients taking aspirin or lipid lowering drugs
9. Obese individuals
10. Surgery in 3 months.
11. Patients having space occupying lesions,
12. Subdural hematoma.

METHODOLOGY

For all the 150 cases admitted ,detailed clinical examination and history regarding smoking, alcohol, diabetes, hypertension, coronary heart disease, renal disease, any infection , surgery, trauma are enquired. Blood sugar ,ECG and routine investigation was done.

Serum fibrinogen was measured in all these 150 patients who are included in the study and the values interpreted.

SERUM FIBRINOGEN

MEASUREMENT OF FIBRINOGEN7, 8

There are many fibrinogen assays available in various laboratory. Out of all the clauss method is the one that is most commonly used to determine serum fibrinogen value in most of the laboratories. Few of the tests are designed for an emergency situation where we need only to know whether the value is elevated or decreased. The exact fibrinogen value is not needed at certain times.

PREREQUISTE

WHO recommends tri-sodium citrate to be used as an anticoagulant for determining serum fibrinogen value. The strength most commonly used is 0.105 to 0.109m.

The sample to be used should contain 1 part of anticoagulant and 9 parts of blood.

Under strict aseptic precautions the blood should be drawn rapidly from the venepuncture site with minimal stasis and transferred to citrated container.

This sample should be inverted gently to look for any clots. In the presence of clot or hemolysis the sample should not be used and discarded as this may interfere

with fibrinogen value. The blood sample collected can be stored

at room temperature.

PREPARATION OF SERUM:

The sample collected should be subjected to centrifuge to remove the platelets . this centrifugation can be performed in room temperature. The resultant serum can be used immediately or stored in deep freeze at -70^0C for maximum of 18 months. The photo optical methods used in determination of fibrinogen may interfere with the samples that are lipaemic or icteric and hence these samples should be avoided.

FIBRINOGEN ASSAYS[9]

1. CLAUSS ASSAYS

It is the most commonly performed method to determine serum fibrinogen value. This test based on the rate of clot formation in dilute citrated serum following the addition of thrombin. The clotting of dilute serum is inversely proportional to the serum fibrinogen

concentration when high concentration of thrombin is used. In this procedure a high concentration of thrombin say 100μ/ml is added to platelet poor plasma and the clotting time is measured.

The high concentration of thrombin that is added to plasma ensures that wide fibrinogen values are independent of thrombin concentration. . The clotting end point is measured by either mechanical or photo-optical means, as these methods have shown excellent crosscorrelation and precision.

The results are plotted in a calibration curve made from clotting times with serial dilution and fibrinogen concentration. The result obtained will be in mg/dl.

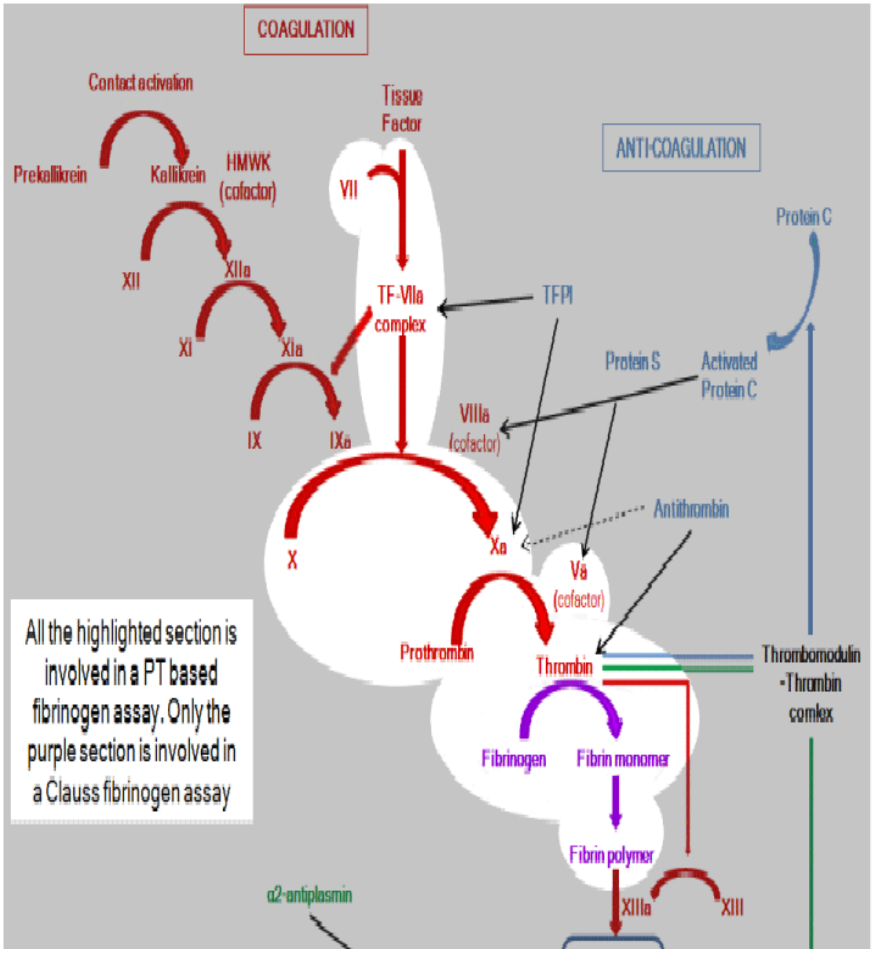
The most frequently used method is that of Von Clauss.. The amount of thrombin chosen ensures that the clotting time is dependant on the fibrinogen level of plasma sample. A high concentration of thrombin (ranging from 35-200μ/ml, but typically about) is added to dilute test plasma and clotting time is measured, result is compared to a calibration curve prepared by clotting a series of

dilutions of a reference serum of known fibrinogen concentration and a result obtained is in mg/dl.

. As this type of assay measures the time to formation of a detectable clot, the presence of inhibitors of fibrin polymerization, such as fibrinogen and14 fibrinogen degradation products results in under estimation of the actual fibrinogen concentration.

PT - BASED TESTS

In this method prothrombin time is determined by optical density change in a platelet poor plasma and compared with derived fibrinogen in a calibration curve.



The other methods to determine fibrinogen include;

1. Gravimetric method

2. Immunological

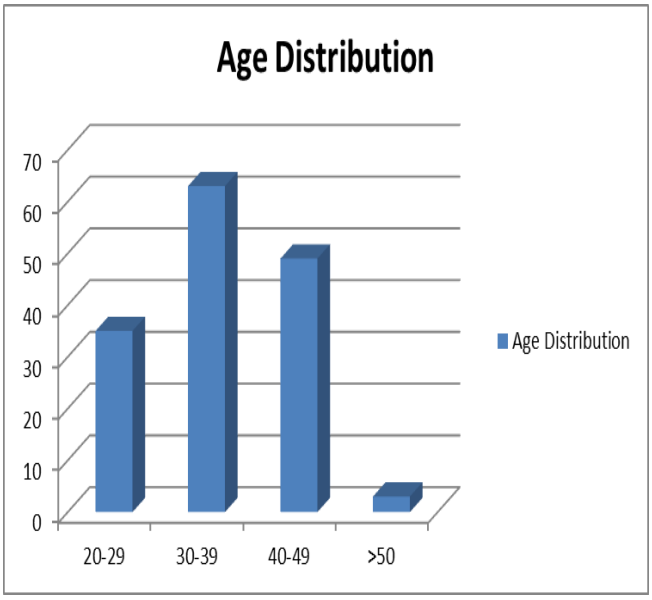
3. Salting out.

OBSERVATION AND RESULTS

1.AGE DISTRIBUTION

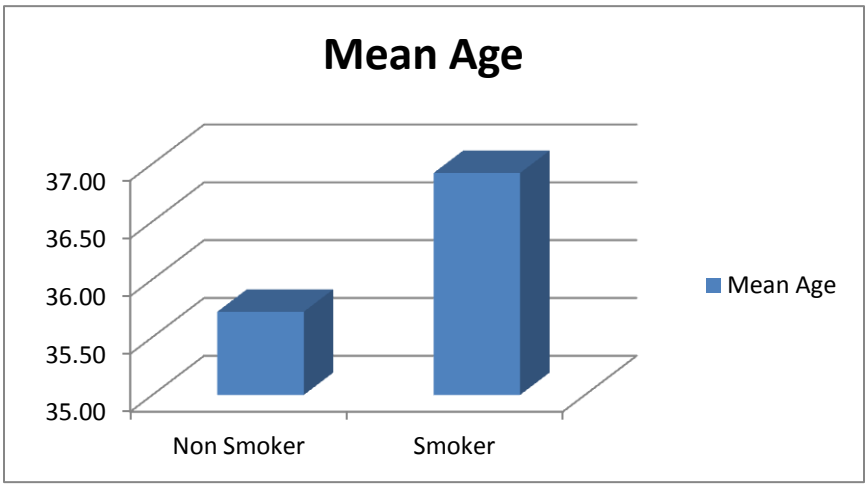
Age Cat

		Age Distribution	Percent	Valid Percent	Cumulative Percent
Valid	20-29	35	23.3	23.3	23.3
	30-39	63	42.0	42.0	65.3
	40-49	49	32.7	32.7	98.0
	>50	3	2.0	2.0	100.0
	Total	150	100.0	100.0	

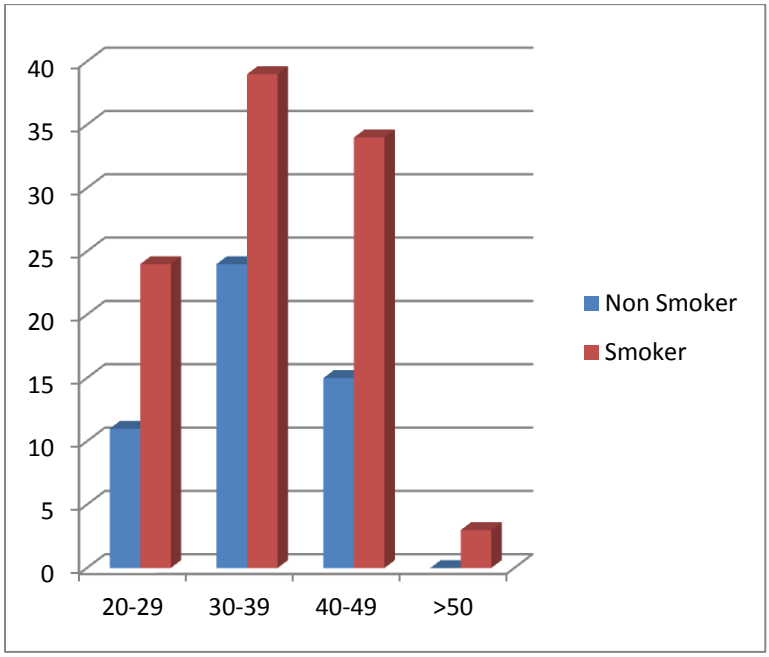


AGE(in years)

Smoker-1 Nonsmoker-0	Mean Age	N	Std. Deviation
Non Smoker	35.72	50	6.743
Smoker	36.92	100	7.770
Total	36.52	150	7.443



	Age Distribution	Smoker-1 Nonsmoker-0		Total
		Non Smoker	Smoker	
Age Cat	20-29	11	24	35
	30-39	24	39	63
	40-49	15	34	49
	>50	0	3	3
Total		50	100	150

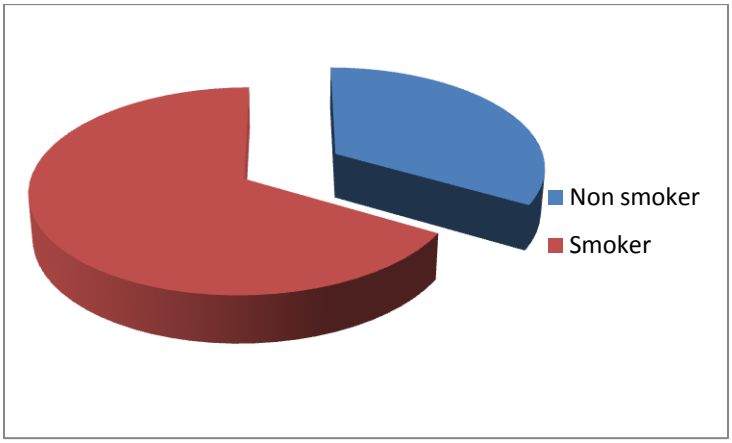


Persons in smoking criteria falls maximally inder the age group between 30 to 39 years of age.The mean age of smokers is 37. The mean age of non smokers is 36. Maximal number of persons in both smoking and non smoking criteria falls between 30 to 39 years of age. P value by chi square method is 0.501 and the symmetrical measure value is 0.078. this proves that simply classifying the people according to age group is of no significance.

2.SMOKER VS NON-SMOKER

Smoker-1 Nonsmoker-0

			Percent	Valid Percent	Cumulative Percent
Valid	Non smoker	50	33.3	33.3	33.3
	Smoker	100	66.7	66.7	100.0
	Total	150	100.0	100.0	



The total numbers of smokers in my study is **100.**

The total number of non smokers in my study is **50.**

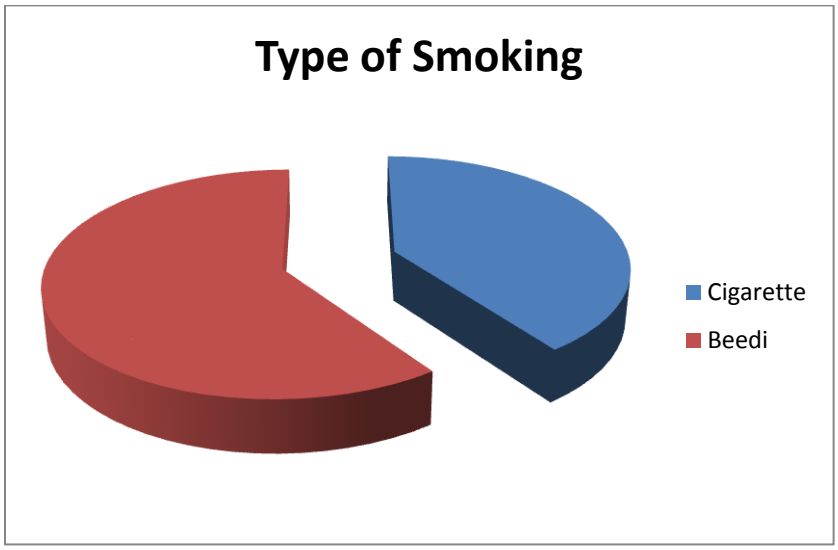
Smokers contributes **66.7%** of my study.

Non smokers contributes **33.3%** of my study.

3.TYPE OF SMOKING

TYPE OF SMOKING Cig0bee1

		Type of Smoking	Percent	Valid Percent	Cumulative Percent
Valid	Cigarette	40	26.7	40.0	40.0
	Beedi	60	40.0	60.0	100.0
	Total	100	66.7	100.0	
Missing	System	50	33.3		
Total		150	100.0		



The total numbers of beedi smokers in my study is **60**. The total number of cigarette smoker is **40**. Cigarette smoker contributes to **40%** of the total 150 persons. Beedi smokers contributes to **26.7%** of total 150 persons.

4.PACKS PER DAY

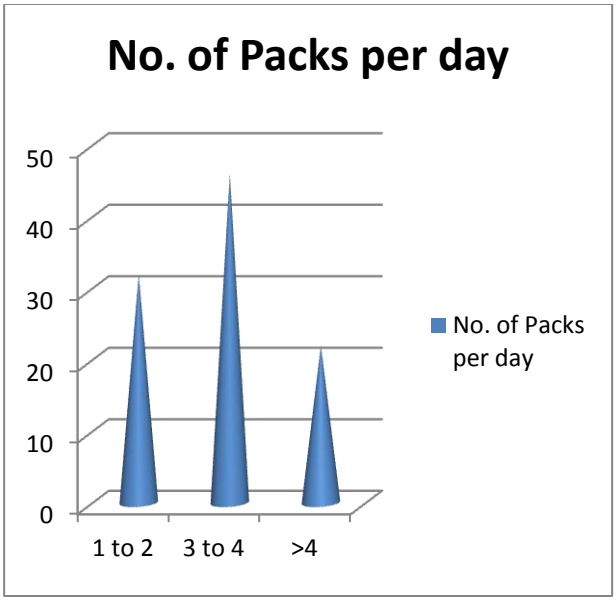
packs cat

		No. of Packs per day	Percent	Valid Percent	Cumulative Percent
Valid	1 to 2	32	21.3	32.0	32.0
	3 to 4	46	30.7	46.0	78.0
	>4	22	14.7	22.0	100.0
	Total	100	66.7	100.0	
Missing	System	50	33.3		
Total		150	100.0		

Report

no of pkts

Mean	N	Std. Deviation
3.26	100	1.440



The maximal number of persons who smoke in my study smokes an average of 3 to 4 packs per day. The mean is 3.26 with a standard deviation of 1.440

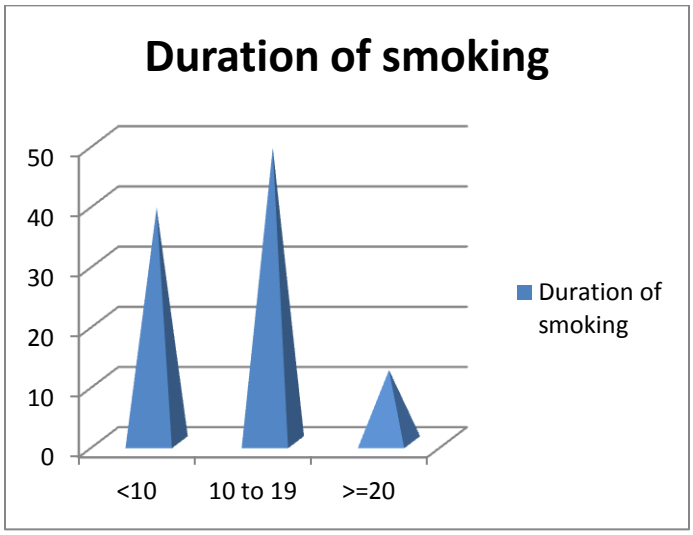
5.DURATION OF SMOKING

duration cat

		Duration of smoking	Percent	Valid Percent	Cumulative Percent
Valid	<10	39	26.0	39.0	39.0
	10 to 19	49	32.7	49.0	88.0
	>=20	12	8.0	12.0	100.0
	Total	100	66.7	100.0	
Missing	System	50	33.3		
Total		150	100.0		

DURATION OF SMOKING

Mean	N	Std. Deviation
12.17	100	6.171



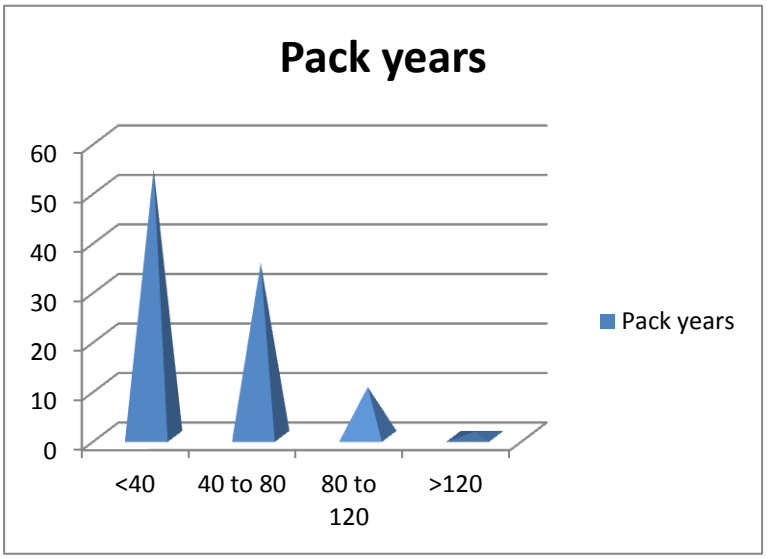
The majority of smokers in my study smokes around **10 to 19 years**. The mean value is **12.17**

with a standard deviation **of 6.17**

6.PACK YEARS

pack years cat

		Pack years	Percent	Valid Percent	Cumulative Percent
Valid	<40	54	36.0	54.0	54.0
	40 to 80	35	23.3	35.0	89.0
	80 to 120	10	6.7	10.0	99.0
	>120	1	.7	1.0	100.0
	Total	100	66.7	100.0	
Missing	System	50	33.3		
Total		150	100.0		



Maximal numer of smokers **<u>54%</u>** in my study smokes are having pack years of **<u>< 40 years</u>**. Only **<u>1%</u>** of the

smokers are having a pack year of **> 120**.

Report

PACK YEARS

Mean	N	Std. Deviation
41.74	100	28.873

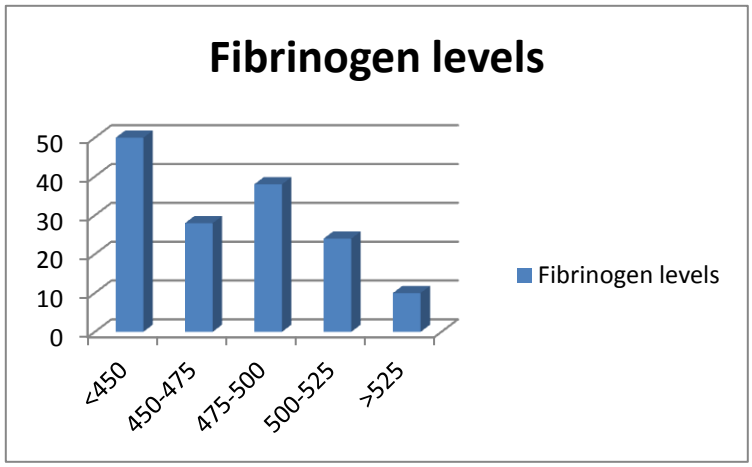
The mean pack years is 41.74 with a standard deviation of

28.873

7.FIBRINOGEN

Fibrin cat

		Fibrinogen levels	Percent	Valid Percent	Cumulative Percent
Valid	<450	50	33.3	33.3	33.3
	450-475	28	18.7	18.7	52.0
	475-500	38	25.3	25.3	77.3
	500-525	24	16.0	16.0	93.3
	>525	10	6.7	6.7	100.0
	Total	150	100.0	100.0	



Crosstab

Count

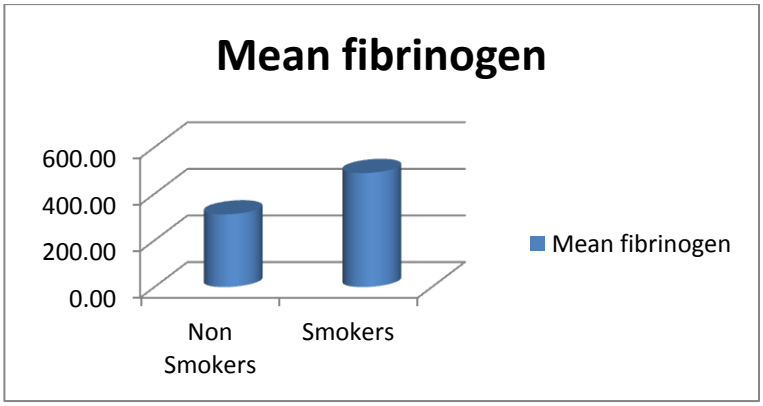
		Smoker-1 Nonsmoker-0		
		Non Smokers	Smokers	Total
Fibrin cat	<450	50	0	50
	450-475	0	28	28
	475-500	0	38	38
	500-525	0	24	24
	>525	0	10	10
Total		50	100	150

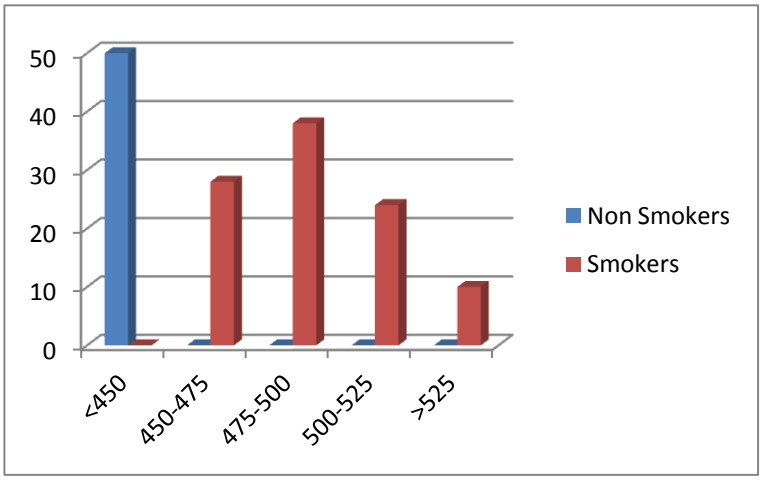
All non smokers have serum fibrinogen value <450 mg%.

Where as majority of the smokers have a serum level of Fibrinogen between 475 to 500 mg%

Fibrin

Smoker-1 Nonsmoker-0	Mean fibrinogen	N	Std. Deviation
Non Smokers	311.92	50	37.101
Smokers	489.51	100	23.875
Total	430.31	150	88.808





The mean serum fibrinogen value in non smokers is 318 mg%.

The mean serum fibrinogen value in smokers is 489 mg.

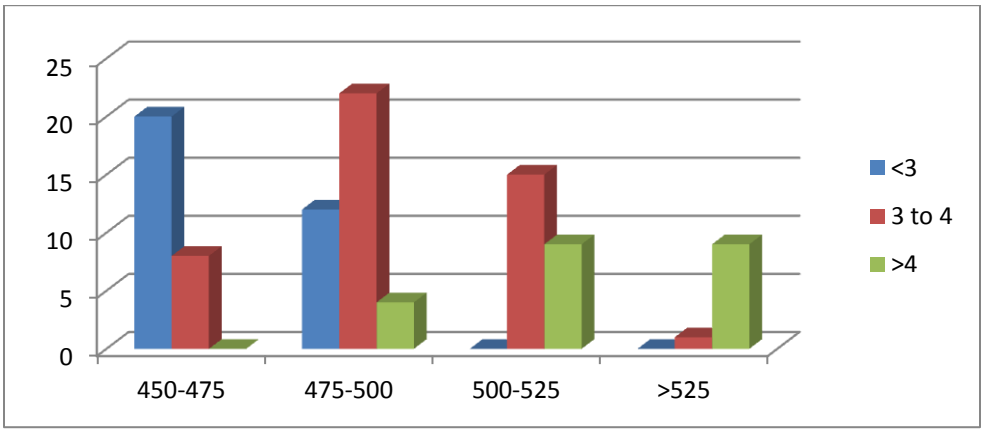
P value is < 0.01. symmetrical measure is 0.706 which proves that the level of serum fibrinogen is smokers is significant and a positive correlation between smoking and

the levels of fibrinogen.

8.PACKS VS FIBRINOGEN

Count

		packs cat			
		<3	3 to 4	>4	Total
Fibrin cat	450-475	20	8	0	28
	475-500	12	22	4	38
	500-525	0	15	9	24
	>525	0	1	9	10
Total		32	46	22	100



Among the smoker who smoke less than 3 packs per day have serum fibrinogen levels

between 450 to 475 mg%. Smokers who smoke more than 4 packs per day have serum

fibrinogen levels between 500 and 525 mg% with a statistical significance of p0.000 which

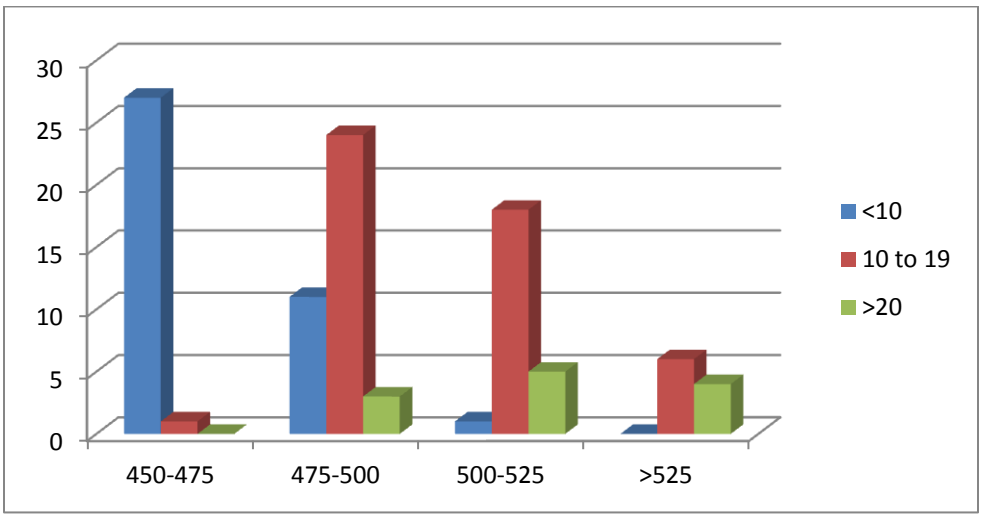
clearly proves that a strong correlation exists between serum fibrinogen levels and the

amount of smoking per day.

9.DURATION VS FIBRINOGEN

Count

		duration cat			
		<10	10 to 19	>20	Total
Fibrin cat	450-475	27	1	0	28
	475-500	11	24	3	38
	500-525	1	18	5	24
	>525	0	6	4	10
Total		39	49	12	100



Among the smoker who have smoked less than 10 years have serum fibrinogen levels

between 450 to 475 mg%. The persons who smoked > 10 years have serum

fibrinogen levels between 500 to 525mg% with a with a statistical significance of p0.000

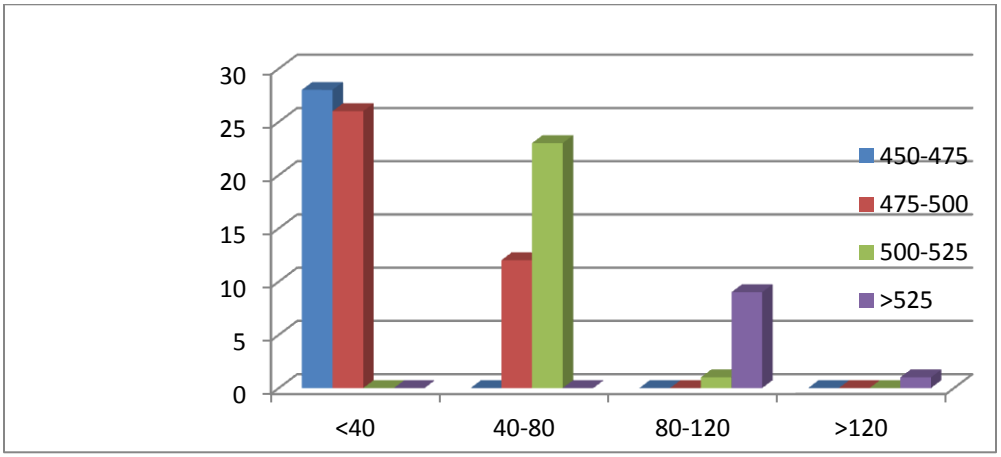
which clearly proves that a strong correlation exists between serum fibrinogen levels and

the duration of smoking.

10.Fibrinogen and pack years:

Count

		pack years cat				
		<40	40-80	80-120	>120	Total
Fibrin cat	450-475	28	0	0	0	28
	475-500	26	12	0	0	38
	500-525	0	23	1	0	24
	>525	0	0	9	1	10
Total		54	35	10	1	100



Among the smoker with pack years less than 40 years have serum fibrinogen levels

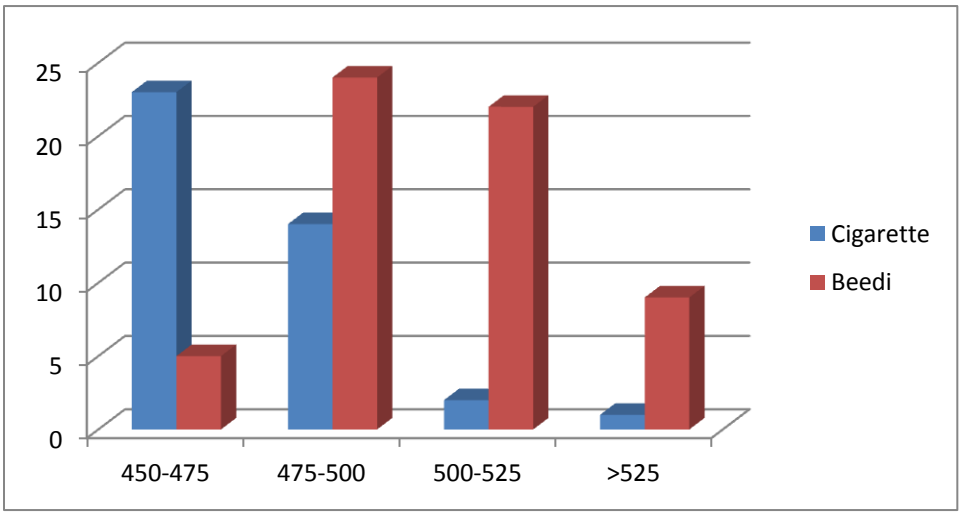
between 450 to 500 mg%. smoker with pack years between 40 to 80 years have serum

fibrinogen levels between 500 to 525 mg%. Smoker with pack years more than

80 years have serum fibrinogen levels more than 525 mg%.

11.Type vs fibrinogen

		TYPE OF SMOKING Cig0bee1		
		Cigarette	Beedi	Total
Fibrin cat	450-475	23	5	28
	475-500	14	24	38
	500-525	2	22	24
	>525	1	9	10
Total		40	60	100



Among the smoker who have have serum fibrinogen levels between 450 to 475 mg% most of them are cigarette smokers. Among the smoker who have have serum fibrinogen levels between 475 to >525 mg% most of them are beedi smokers . this result has a statistical significance of p value0.000 which proves that the result is significant

.

12.REPORT

Report

TYPE OF SMOKING Cig0bee1		AGE(in years)	no of pkts	DURATION OF SMOKING	PACK YEARS	Fibrin	CT	aPTT(secs)	CRP(mg/l)
Cigarette	Mean	30.00	2.65	8.08	23.10	473.35	352.90	30.95	4.25
	N	40	40	40	40	40	40	40	40
	Std. Deviation	4.315	1.442	4.178	19.052	18.137	36.986	.986	.954
Beedi	Mean	41.53	3.67	14.90	54.17	500.28	296.48	29.75	5.52
	N	60	60	60	60	60	60	60	60
	Std. Deviation	5.907	1.298	5.780	27.682	21.071	43.278	.968	1.127
Total	Mean	36.92	3.26	12.17	41.74	489.51	319.05	30.23	5.01
	N	100	100	100	100	100	100	100	100
	Std. Deviation	7.770	1.440	6.171	28.873	23.875	49.261	1.136	1.227

DISCUSSION

DISCUSSION:

This study is mainly done because the habit of smoking is very common in our culture. Almost every men living in my place had a habit of smoking. They are also more prone for the adverse effects of smoking. Along with smoking they are are also more prone for developing other habits like alcoholism and drug abuse. One of the main adverse effect of smoking is myocardial infarction. The main substance present in smoking responsible for producing the adverse effect of smoking is nicotine.

The main way by which smoking produces smoking is by inflammation. One of the main substance that is produced during inflammation is fibrinogen. It is mainly responsible for the adverse effects of smoking like myocardial infarction , stroke and other thrombotic episodes. Therefore this study is carried out to find out the levels of serum fibrinogen in the smokers and to compare the levels of fibrinogen according to the type , duration and amount of smoking.

The results of the study are interrupted here below.

TABLE 1 shows Persons in smoking criteria falls maximally inder the age group between 30 to 39 years of age.The mean age of smokers is 37. The mean age of non smokers is 36. Maximal number of persons in both smoking and non smoking criteria falls between 30 to 39 years of age. P value by chi square method is 0.501 and the symmetrical measure value is 0.078. this proves that simply classifying the people according to age group is of no significance.

TABLE 2 shows The total numbers of smokers in my study is **100.** The total number of non smokers in my study is **50.**

Smokers contributes **66.7%** of my study.

Non smokers contributes **33.3%** of my study.

TABLE 3 shows The total numbers of beedi smokers in my study is **60**. The total number of cigarette smoker is **40**.

Cigarette smoker contributes to **40%** of the total 150 persons. Beedi smokers contributes to **26.7%** of total 150 persons.

TABLE 4 shows The maximal number of persons who smoke in my study smokes an average of 3 to 4 packs per day. The mean is 3.26 with a standard deviation of 1.440

TABLE 5 shows The majority of smokers in my study smokes around **10 to 19 years**. The mean value is **12.17** years with a standard deviation **of 6.17.**

TABLE 6 shows Maximal numer of smokers **54%** in my study are having pack years of **< 40 years**. Only **1%** of the smokers are having a pack year of **> 120**.

The mean pack years is 41.74 with a standard deviation of 28.873

TABLE 7 Shows All non smokers have serum fibrinogen value <45 mg%. Where as majority of the smokers have a serum level of Fibrinogen between 475 to 500 mg%

The mean serum fibrinogen value in non smokers is 318 mg%.

The mean serum fibrinogen value in smokers is 489 mg.

P value is < 0.01. symmetrical measure is 0.706 which proves that the level of serum fibrinogen is smokers is significant and a positive correlation between smoking and the levels of fibrinogen

.

TABLE 8 shows Among the smoker who smoke less than 3 packs per day have serum fibrinogen levels between 450 to 475 mg%.

Smokers who smoke more than 4 packs per day
have serum fibrinogen levels between 500 and 525 mg% with a statistical significance of p0.000 which clearly proves that a strong correlation exists between serum fibrinogen levels and the amount of smoking per day

TABLE 9 shows Among the smoker who have smoked less than 10 years have serum fibrinogen levels between 450 to 475 mg%. The persons who smoked > 10 years have serum fibrinogen levels between 500 to 525mg% with a with a statistical significance of p0.000 which clearly proves that a strong correlation exists between serum fibrinogen levels and the duration of smoking

TABLE 10 showsAmong the smoker with pack years less than 40 years have serum fibrinogen levels between 450 to 500 mg%. smoker with pack years between 40 to 80 years have serum fibrinogen levels between 500 to 525 mg%. Smoker with pack years more than 80 years have serum fibrinogen levels more than 525 mg%.

TABLE 11 shows Among the smoker who have have serum fibrinogen levels between 450 to 475 mg% most of them are cigarette smokers.

Among the smoker who have have serum fibrinogen levels

between 475 to >525 mg% most of them are beedi smokers .

this result has a statistical significance of p value0.000

which proves that the result is significant.

CONCLUSION

Conclusion:

1. Serum level of fibrinogen in smokers is significantly higher than in nonsmokers.
2. Higher level of Smoking is associated with lower value of APTT.
3. Higher level of smoking is associated with higher levels of CRP.
4. Smokers who smoke more cigarettes or beedis per day have higher levels of serum fibrinogen.
5. Smokers having higher pack years have higher levels of fibrinogen.
6. Beedi smokers have higher levels of serum fibrinogen.

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ANNEXURE 1

A STUDY ON SERUM LEVELS OF FIBRINOGEN IN SMOKERS:

PROFORMA:

Date:

Name:

Age:

Height:

Weight:

History of presenting illness:

History of past illness:

H/o diabetes:

H/o hypertension:

H/o tuberculosis:

H/o CAHD:

H/o CVA:

H/o liver , kidney , thyroid disease:

H/o DVT:

H/o drug intake:

Personal history:

Smoking:

Type:

Amount:

Duration:

Alcoholism:

Drug abuse:

General examination:

Pulse:

Bp:

Respiratory rate:

Temperature:

CVS:

RS:

Abdomen:

CNS:

Investigations:

CBC:

TC:

DC:

ESR:

Hb:

Platlets:

Urea:

Creatinine:

Blood sugar:

Lipid profile:

CRP:

Clotting time:

APTT:

Serum fibrinogen:

ANNEXURE 2:

MASTER CHART OF CONTROL:

S.NO	NAME	AGE(in years)	SERUM CHOLESTEROL(in mg/dl)	RBS(mg/dl)	UREA(mg/dl)	CREATININE(mg/d	BLOOD PRESSURE(in mm of H	LDL(in mg/dl)	TDL(in mg/dl)	ECG	CLOTTING TIME(in sec	aPTT(in sec	CRP(mg/l	PAST hfa TIA	PAST hfa STROK	PAST hfa MI	PAST hfa D
1	Valu	31	250	117	27	1.3	120/80	120	142	within normal limits	190	38	0.2	na	na	na	na
2	Pitchiah	40	304	111	29	1	130/70	103	110	within normal limits	234	42	0.5	na	na	yes	na
3	Sikandar	26	206	124	33	1.1	110/80	114	116	within normal limits	210	39	0.6	na	na	na	na
4	Krishnan	30	302	136	22	1	120/80	112	123	within normal limits	313	41	0.9	na	na	na	na
5	Pannanpalam	41	296	119	30	1.4	110/80	125	143	within normal limits	347	40	0.3	na	na	yes	na
6	Akilan	32	254	125	21	0.8	110/80	106	121	within normal limits	278	38	0.1	na	na	na	na
7	Sudharaman	27	318	112	39	0.6	140/90	111	102	within normal limits	241	39	0.4	na	na	na	na
8	Challapa	31	337	130	29	1.1	130/80	117	116	within normal limits	206	41	0.6	na	na	na	na
9	Muppidathi	42	270	127	23	1	110/70	119	124	within normal limits	310	40	0.9	yes	na	yes	na
10	Marimuthu	28	301	110	38	1.1	130/90	125	139	within normal limits	284	42	0.7	na	na	na	na
11	Hameed	32	285	123	22	0.9	140/90	113	131	within normal limits	313	39	0.3	na	na	na	na
12	Rajan	33	307	134	24	0.6	140/90	107	148	within normal limits	320	38	0.5	na	na	na	na
13	Rakesh	43	328	129	40	0.8	140/90	128	117	within normal limits	339	39	0.4	na	na	yes	na
14	Alagaiah	36	299	133	26	1	110/70	109	110	within normal limits	339	38	0.6	na	na	na	yes
15	Nainar	29	296	126	21	1.4	120/70	114	125	within normal limits	267	41	0.9	na	na	na	na
16	Maduramy	33	340	137	36	1.1	130/80	115	129	within normal limits	305	39	0.8	na	na	na	na
17	Mahesh	34	313	112	29	1	120/70	106	135	within normal limits	341	42	0.2	na	na	na	na
18	Stalin	49	283	129	33	1.4	110/80	119	129	within normal limits	394	39	0.9	yes	na	yes	na
19	Mankaiah	39	302	114	23	1.2	120/80	109	112	within normal limits	358	40	0.3	na	na	yes	na
20	Ravi	30	258	128	27	1.3	120/80	127	120	within normal limits	327	38	1	na	na	na	na
21	Edwin	28	324	127	30	0.8	140/90	125	138	within normal limits	274	38	0.4	na	na	na	na
22	Balaji	35	349	124	34	0.6	110/70	117	133	within normal limits	229	41	0.5	na	na	na	na
23	Karuppasamy	38	313	134	22	1.1	120/80	108	129	within normal limits	346	39	0.2	na	na	yes	na
24	Arumugam	37	270	128	32	0.6	110/70	129	130	within normal limits	379	38	0.7	yes	na	na	na
25	Duraidass	48	340	115	35	1.4	120/80	104	105	within normal limits	401	42	0.8	na	na	yes	yes
26	Ayyasamy	26	376	132	28	1	130/80	127	101	within normal limits	224	41	0.6	na	na	na	na
27	Gopal	36	347	139	39	1	110/70	117	137	within normal limits	271	40	0.3	na	na	yes	na
28	Sakthi	47	327	136	20	0.7	110/80	115	141	within normal limits	317	38	0.2	na	na	yes	na
29	Ezhil	33	340	112	33	0.8	120/80	104	98	within normal limits	260	39	0.5	na	na	na	na
30	Vikram	27	359	121	29	1.1	130/80	118	129	within normal limits	212	39	0.8	na	na	na	na
31	Vel	30	375	125	37	1.3	130/80	130	136	within normal limits	285	42	0.7	na	na	na	na
32	Ganesh	46	335	133	33	0.6	140/90	129	125	within normal limits	377	41	0.4	yes	na	na	na
33	Mariappan	29	290	138	27	1.1	130/90	110	102	within normal limits	254	39	0.3	na	na	na	na
34	Kumar	35	331	120	32	1	120/80	121	135	within normal limits	340	38	0.6	na	na	na	na
35	Sundar	45	317	111	21	0.8	120/70	116	147	within normal limits	395	41	0.5	na	na	yes	na
36	Maurthy	39	282	122	22	0.9	130/80	104	119	within normal limits	350	40	0.9	na	na	na	yes
37	Vijay	38	259	135	37	0.7	110/70	123	107	within normal limits	299	39	0.6	na	na	na	na
38	Sakapathi	29	340	138	34	0.9	110/80	101	125	within normal limits	263	38	0.8	na	na	na	na
39	Prakash	44	289	113	20	1.3	140/90	127	111	within normal limits	207	42	0.2	na	na	yes	na
40	Thangadurai	34	294	127	39	1.1	110/70	114	139	within normal limits	372	41	0.8	na	na	na	na
41	Jashva	26	318	122	21	1.4	130/80	124	144	within normal limits	206	42	0.9	na	na	na	na
42	Ashok	39	356	135	26	1.2	140/80	111	129	within normal limits	391	40	0.3	na	na	yes	na
43	Elumalai	44	333	119	38	1.1	110/80	126	140	within normal limits	393	38	0.7	na	na	yes	na
44	Ranjith	31	273	122	27	0.6	120/70	109	133	within normal limits	203	39	1	na	na	na	na
45	Mankandi	47	259	132	25	0.9	130/80	105	142	within normal limits	329	41	0.9	na	yes	na	na
46	Kamaraj	40	371	111	20	1.3	120/70	123	127	within normal limits	323	39	0.6	yes	na	na	na
47	Palavesam	42	261	122	28	0.8	130/70	115	101	within normal limits	316	40	0.2	na	na	yes	na
48	Muthukumar	46	342	124	33	0.8	140/90	130	113	within normal limits	379	38	0.4	na	na	yes	yes
49	Shiva	29	253	110	21	1.2	130/80	110	119	within normal limits	299	40	0.8	na	na	na	na

Master chart of cases

.NO	NAME	AGE(in years)	TYPE OF SMOKING	no of pkts	DURATION OF SMOKING	PACK YEARS	FIBRINOGEN(in mg/dl)	RBS(mg/dl)	UREA(mg/dl)	CREATININE(mg/dl)	BLOOD PRESSURE(in mm of Hg)	LDL(in mg/dl)	TDL(in mg/dl)	ECG	CLOTTING TIME(secs)	aPTT(secs)	CRP(mg/l)	PAST h/o TIA	PAST h/o STROKE	PAST h/o MI	PAST h/o DVT
1	Ramesh	27	cigarette	2	7	14	462	127	28	0.7	120/70	117	131	within normal limits	363	31	3.8	no	no	no	no
2	Alagaiah	47	beedi	3	20	60	509	139	31	0.9	140/90	121	105	within normal limits	284	30	6	yes	no	yes	no
3	Muthupandi	42	beedi	1	15	15	464	140	35	1	130/80	104	117	within normal limits	360	31	3.9	no	yes	yes	no
4	Selvam	30	cigarette	4	10	40	491	120	22	1.2	110/70	127	135	within normal limits	318	30	5.1	no	no	no	no
5	Raja	32	beedi	3	9	27	477	135	20	1.1	130/70	129	121	within normal limits	342	31	4.4	no	no	no	no
6	Duraisamy	39	beedi	5	12	60	509	121	39	1.4	140/80	110	126	within normal limits	284	30	5.8	yes	yes	no	yes
7	Velu	29	cigarette	2	5	10	460	117	21	0.8	110/80	115	142	within normal limits	366	31	3.6	no	no	no	no
8	Shiva	25	cigarette	2	4	8	459	111	27	0.6	120/80	121	110	within normal limits	384	32	3.4	no	no	no	no
9	Karthikeyan	28	cigarette	4	3	12	462	124	28	0.8	110/70	125	116	within normal limits	365	32	3.7	no	no	no	no
10	Muthaiah	44	beedi	6	17	102	532	136	31	0.9	130/80	118	123	within normal limits	228	28	7.3	yes	yes	no	yes
11	Kasidas	47	beedi	5	14	70	515	119	23	1.1	140/90	130	143	within normal limits	266	29	6.4	no	yes	yes	no
12	Thiruselvam	34	beedi	3	6	18	470	125	36	1	130/70	101	121	within normal limits	358	31	4	no	no	no	yes
13	Suresh	36	beedi	2	12	24	475	112	25	0.9	130/70	107	102	within normal limits	347	31	4.5	no	no	yes	no
14	Ganesan	41	beedi	3	8	24	475	138	39	0.6	130/80	111	116	within normal limits	345	31	4.4	yes	no	yes	no
15	Pandaram	48	beedi	4	14	56	505	127	26	0.8	140/80	123	124	within normal limits	290	29	5.4	yes	yes	yes	no
16	Krishnasamy	49	beedi	5	22	110	535	110	31	1	140/90	106	139	within normal limits	212	28	7.5	no	yes	no	no
17	Subaiah	32	beedi	6	11	66	512	123	28	1.3	120/80	119	131	within normal limits	278	29	6.3	no	no	yes	no
18	Muthukumar	37	beedi	3	4	12	462	134	36	1.3	130/70	126	148	within normal limits	363	32	3.7	no	no	no	no
19	Tamilarasan	31	beedi	3	14	42	493	129	29	0.6	110/80	130	117	within normal limits	313	30	5.4	no	no	no	no
20	Manohar	38	beedi	2	21	42	493	133	33	1.1	120/80	103	110	within normal limits	313	30	5.3	no	yes	yes	no
21	Kaviyaraja	26	cigarette	1	7	7	459	126	19	0.9	110/80	114	125	within normal limits	384	32	3.4	no	no	no	no
22	Pandian	43	beedi	7	13	91	529	137	22	1.2	110/80	112	129	within normal limits	238	29	6.9	no	no	yes	no
23	Jeyaram	45	beedi	5	18	90	529	112	34	1.4	140/90	125	135	within normal limits	236	29	6.8	no	yes	yes	no
24	Bharathi	36	cigarette	3	16	48	498	129	27	1.3	130/80	106	139	within normal limits	304	30	5.4	yes	no	no	no
25	Thayappa	28	cigarette	1	5	5	457	114	29	1	110/70	111	118	within normal limits	392	32	3.3	no	yes	no	no
26	Senthil kumar	39	beedi	5	9	45	495	128	33	1.1	130/90	117	116	within normal limits	307	30	5.5	no	no	no	yes
27	Karthikeyan	44	beedi	3	19	57	507	127	22	1	140/90	119	104	within normal limits	286	30	5.8	yes	no	no	no
28	Solomon	49	beedi	4	12	48	498	130	38	1.4	140/90	125	99	within normal limits	304	30	5.4	no	no	yes	yes
29	Arputham	26	cigarette	2	9	18	470	135	21	0.8	140/90	113	127	within normal limits	358	31	4	no	no	no	no
30	Devaraj	47	beedi	3	16	48	498	111	39	0.6	110/70	107	109	within normal limits	302	30	5.3	no	yes	yes	no
31	Ajith	25	cigarette	1	2	2	450	139	29	1.1	120/70	100	118	within normal limits	410	32	3	no	no	no	no
32	Soundararajan	34	cigarette	3	12	36	487	129	23	1	130/80	123	114	within normal limits	328	31	4.9	no	no	yes	no
33	Mahesh	38	beedi	4	19	76	520	123	38	1.1	130/70	111	142	within normal limits	258	29	6.6	no	no	yes	no
34	Aarumugam	28	cigarette	2	7	14	462	119	22	0.9	110/80	116	139	within normal limits	363	32	3.7	yes	no	no	no
35	Palanivel	37	beedi	5	15	75	517	121	24	0.6	120/80	118	136	within normal limits	262	29	6.4	yes	no	no	no
36	Muthukumar	43	beedi	3	9	27	477	128	40	0.8	120/80	124	129	within normal limits	342	31	4.4	no	yes	yes	no
37	Sakthivel	29	cigarette	2	3	6	457	130	26	1	140/90	129	104	within normal limits	392	32	3.5	no	yes	no	no
38	Daniel raja	37	beedi	5	15	75	517	133	21	1.4	110/70	126	107	within normal limits	262	29	6.4	no	no	yes	no
39	Sabari	45	beedi	2	19	38	489	117	36	1.1	120/80	102	117	within normal limits	322	30	4.9	yes	yes	no	no
40	Kannan	42	beedi	3	12	36	487	124	29	1	130/80	116	108	within normal limits	328	30	4.7	yes	no	yes	no
41	Veerapandi	49	beedi	4	16	64	512	139	33	1.4	140/90	105	102	within normal limits	277	29	6.3	yes	yes	yes	no
42	Pitchiah	39	cigarette	6	14	84	525	132	23	1.2	130/80	123	133	within normal limits	251	29	6.7	no	no	yes	no
43	Kumar	28	cigarette	1	7	7	459	120	27	1.3	110/70	112	137	within normal limits	384	32	3.5	no	no	no	no
44	Prakash	33	beedi	3	9	27	477	119	30	0.8	120/70	104	136	within normal limits	342	31	4.4	no	no	no	no
45	Senthil	45	beedi	5	11	55	505	110	34	0.6	130/70	126	129	within normal limits	290	29	5.5	no	no	yes	yes
46	Amalan	49	beedi	4	18	72	515	124	22	1.1	140/90	107	104	within normal limits	266	29	6.4	no	yes	yes	no
47	Chellapa	36	beedi	2	13	26	477	134	32	0.6	120/80	128	124	within normal limits	343	31	4.3	no	no	yes	no
48	Anand	28	cigarette	3	4	12	462	128	35	1.4	110/70	109	111	within normal limits	362	31	3.7	no	no	no	no
49	Jeyaraj	38	beedi	5	6	30	482	115	28	1	130/80	114	118	within normal limits	340	31	4.7	yes	no	yes	no
50	Lingeswaran	42	beedi	4	10	40	491	132	22	1.2	130/90	113	120	within normal limits	318	30	5	no	no	no	yes
51	Tirupathi	40	beedi	2	14	28	477	139	29	0.7	130/80	106	117	within normal limits	342	31	4.4	no	no	yes	no
52	Mohan	26	cigarette	1	6	6	457	136	33	0.6	100/70	119	127	within normal limits	392	32	3.5	no	no	no	no
53	Venkatesh	31	cigarette	3	10	30	482	112	39	0.8	110/70	109	131	within normal limits	341	30	4.6	no	no	no	no
54	Kathir	30	cigarette	5	9	45	495	121	31	0.9	120/80	127	140	within normal limits	307	30	5.4	no	no	no	no
55	Harish	26	cigarette	4	5	20	472	125	37	1.1	130/80	125	133	within normal limits	354	31	4.1	no	no	no	no
56	Kutty	33	cigarette	3	11	33	485	133	22	1.4	140/80	117	112	within normal limits	335	30	4.7	no	no	yes	no
57	Sundaramoorth	31	cigarette	1	8	8	459	138	22	1.2	140/90	108	120	within normal limits	384	32	3.5	no	no	yes	no
58	Paulraj	38	beedi	2	13	26	475	120	25	1.2	130/80	129	138	within normal limits	347	31	4.5	yes	no	yes	no
59	Elango	29	cigarette	4	8	32	482	111	33	1	110/70	104	133	within normal limits	340	30	4.7	no	yes	no	no
60	Ravichandran	40	beedi	4	16	64	512	122	27	1.1	120/80	123	129	within normal limits	278	29	6.1	yes	no	yes	no
61	Nainar	36	beedi	3	11	33	485	135	39	1	130/80	119	130	within normal limits	335	30	4.8	no	no	yes	yes
62	Ganeshamoorth	26	cigarette	4	4	16	464	138	24	0.7	110/70	106	105	within normal limits	360	31	3.7	no	no	no	no
63	Prabhu	25	cigarette	1	2	2	450	113	21	0.9	110/80	127	101	within normal limits	410	32	3	no	no	no	no
64	Immanueal	34	beedi	2	9	18	470	127	36	0.8	120/80	112	137	within normal limits	358	31	4	yes	no	yes	no
65	Narayanan	41	beedi	5	19	95	530	122	40	1.2	130/80	107	141	within normal limits	230	28	7.1	no	no	no	yes
66	Prakasam	35	beedi	4	14	56	505	135	33	0.6	130/80	105	98	within normal limits	290	29	5.7	no	no	yes	no
67	Alagesan	48	beedi	3	12	36	487	119	28	0.9	140/90	113	129	within normal limits	328	30	4.7	yes	no	yes	no
68	Stalin	32	cigarette	2	14	28	477	122	32	0.7	130/90	121	136	within normal limits	345	31	4.4	no	no	no	no
69	Pechimuthu	37	cigarette	3	11	33	485	132	22	1.4	120/80	103	125	within normal limits	333	30	4.6	no	no	no	yes
70	Sebastian	30	cigarette	2	9	18	470	111	34	1.1	120/70	116	102	within normal limits	358	31	4	no	no	no	no
71	Thangaraj	44	beedi	4	13	52	500	122	27	0.8	130/80	118	135	within normal limits	297	30	5.5	no	yes	yes	no
72	Kumaresan	26	cigarette	1	8	8	459	124	24	1.2	110/70	123	147	within normal limits	384	32	3.4	no	no	no	no
73	Aravind	33	beedi	5	7	35	487	110	31	0.6	110/80	130	119	within normal limits	323	30	4.7	yes	no	yes	no
74	Velaiah	50	beedi	3	27	81	521	134	39	1	140/90	101	107	within normal limits	255	29	6.6	yes	yes	yes	no
75	Gopinath	26	cigarette	1	5	5	457	118	20	0.7	110/70	127	125	within normal limits	392	32	3.3	no	no	no	no
76	Gnyanasekar	47	beedi	2	21	42	493	133	33	0.8	130/80	114	111	within normal limits	313	30	5.4	no	yes	yes	no
77	Arulraj	29	cigarette	4	6	24	475	136	29	1.1	140/80	124	139	within normal limits	347	31	4.4	no	no	no	no
78	Praveen	25	beedi	3	4	12	462	131	37	1.3	110/80	111	144	within normal limits	363	31	3.7	no	no	no	no
79	Lenin	35	beedi	2	14	28	477	138	33	0.6	120/70	126	129	within normal limits	341	31	4.4	yes	no	yes	no
80	Abdul	44	beedi	5	20	100	532	117	27	1.1	130/80	109	117	within normal limits	227	29	7.3	no	yes	yes	no
81	Madsamy	27	cigarette	1	6	6	457	125	32	1	120/70	105	132	within normal limits	391	32	3.4	no	no	no	no
82	Kavi	31	cigarette	4	9	36	489	121	21	0.8	130/70	123	121	within normal limits	322	30	4.9	no	no	no	no
83	Balaji	41	beedi	3	18	54	502	110	22	0.9	140/90	115	139	within normal limits	294	29	5.6	no	no	yes	yes
84	Pitchaiah	48	beedi	3	13	39	490	112	37	0.7	130/80	130	101	within normal limits	320	30	5	no	yes	yes	no
85	Appukutty	39	cigarette	2	16	32	482	139	34	0.9	120/80	110	138	within normal limits	342	30	4.6	no	no	yes	no
86	Mohideen	45	beedi	5	19	95	530	120	20	1.3	130/80	121	105	within normal limits	230	28	7	yes	no	no	no
87	Thangapandi	37	beedi	6	10	60	509	135	39	1.1	130/70	119	143	within normal limits	284	29	5.9	yes	no	yes	no
88	Kandasamay	45	beedi	3	22	66	512	117	21	1.4	140/80	118	127	within normal limits	278	29	6.1	no	yes	yes	no
89	Elumalai	38	cigarette	4	11	44	495	123	26	1.2	140/90	127	109	within normal limits	307	30	5.4	no	no	no	no
90	Kamaraj	26	cigarette	4	4	16	464	111	38	1.1	110/70	117	117	within normal limits	360	31	3.8	no	no	no	no
91	Joseph	50	beedi	5	29	145	550	116	27	0.6	140/90	115	128	within normal limits	180	28	7.9	yes	yes	yes	no
92	Palavesam	34	cigarette	4	17	68	513	127	25	0.9	130/80	104	148	within normal limits	275	29	6.1	yes	no	no	no
93	Ezhil	49	beedi	3	24	72	515	136	20	1.3	140/90	118	131	within normal limits	266	29	6.3	yes	yes	yes	no
94	Sridhar	47	beedi	2	20	40	491	110	28	0.8	130/80	130	140	within normal limits	318	30	5	no	no	yes	yes
95	Chellaiah	44	beedi	3	26	78	521	115	33	0.8	120/70	129	133	within normal limits	255	29	6.6	yes	no	yes	no
96	Stephen	27	cigarette	1	3	3	454	126	21	1.3	110/80	110	142	within normal limits	398	32	3.2	no	yes	no	no
97	Muniyasamy	38	cigarette	2	17	34	489	116	29	0.6	130/70	121	127	within normal limits	322	30	4.9	no	no	yes	no
98	Kadher	48	beedi	5	12	60	509	124	35	1.4	130/80	116	101	within normal limits	284	29	5.9	yes	no	yes	yes
99	Karupaiah	37	cigarette	6	9	54	502	129	22	1.2	130/80	104	113	within normal limits	293	29	5.6	no	no	no	yes
100	Palanisamy	50	beedi	3	29	87	527	133	30	1	140/90	123	119	within normal limits	247	30	6.8	yes	no	yes	no

ANNEXURE 3:

KEY TO MASTER CHART:

Types of smoking:

0: Cigarette

1: Beedi

Pack years: Duration of smoking in years x no of packs of cigarettes / beedis per day.

CRP: Normal value <1mg / dl.

Clotting time: Normal value 120 to 360 seconds.

APTT: Normal value 27 to 35 seconds

Urea: Normal value in male 7 to 20 mg / dl.

Creatinine: Normal value in males 0.6 to 1.2 mg /dl.

LDL cholesterol, mg/dL (mmol/L)	
<70 (<1.81)	Therapeutic option for very high risk patients
<100 (<2.59)	Optimal
100–129 (2.59–3.34)	Near optimal/above optimal
130–159 (3.36–4.11)	Borderline high
160–189 (4.14–4.89)	High
190 (4.91)	Very high
Total cholesterol, mg/dL (mmol/L)	
<200 (<5.17)	Desirable
200–239 (5.17–6.18)	Borderline high
240 (6.21)	High
HDL cholesterol, mg/dL (mmol/L)	
<40 (<1.03)	Low
60 (1.55)	High

Serum fibrinogen: normal value 200 to 400 mg /dl.

ANNEXURE 4:

ABBREVATIONS:

CT: clotting time

APTT: Activated Partial Thromboplastic Time

CRP: C Reactive Protein

TC: Total Count

DC: Differential Count

ESR: Erythrocyte Sedimentation Rate

HB: Hemoglobin

CAD: Coronary Artery Disease

DVT: Deep Venous Thrombosis